

Organic Reactions

Organic Reactions

VOLUME 14

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the investigator will be able

to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

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CHAPTER I

THE CHAPMAN REARRANGEMENT

J. W. SCHULENBERG AND S. ARCHER

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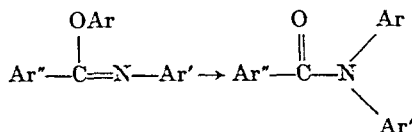
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INTRODUCTION

The thermal conversion of aryl N-arylbenzimidates to N-aroilydiphenyl-



amines is known as the Chapman rearrangement. The rearrangement was discovered by Mumm, Hesse, and Volquartz who, in 1915, described the rearrangement of the parent compound, phenyl N-phenylbenzimidate, to N-benzoyldiphenylamine.¹ No further examples of the reaction were reported until 1925, when Chapman's first study was published.² Since he not only studied the mechanism of the reaction³ but also first used it as a general synthesis of diphenylamines,⁴ his name is associated with this reaction.*

The starting materials for the Chapman rearrangement have been referred to as imino ethers, imido esters, imidates, and by a miscellany of other names. We agree with the recommendations of Roger and Neilson⁶ and have named all compounds as imidates, i.e., as esters of the parent imidic acid. Thus compound 1, when named as a derivative of

¹ Mumm, Hesse, and Volquartz, *Ber.*, **48**, 379 (1915).

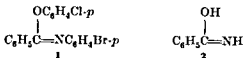
² Chapman, *J. Chem. Soc.*, **127**, 1992 (1925).

³ Chapman, *J. Chem. Soc.*, **1927**, 1743.

⁴ Chapman, *J. Chem. Soc.*, **1929**, 569.

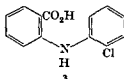
* A broader definition which includes the rearrangement of alkyl imidates has been used.^{5,6} We prefer the more limited one for the following reasons. (1) It is in better accord with general literature usage; Müller⁷ and Gowan and Wheeler⁸ employ the more restricted version. (2) Mechanistically, the rearrangement of aryl benzimidates is distinctly different from that of the alkyl esters. (3) Chapman himself confined his investigations, with one exception, to aryl imidates.

benzimidic acid (2), is called *p*-chlorophenyl *N*-(*p*-bromophenyl)benzimidic acid.



ide, in accordance with *Chemical Abstracts* usage. When named as an imino ether, the compound is called *N*-(*p*-bromophenyl)benzimidino *p*-chlorophenyl ether.

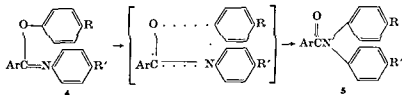
We have not named the rearrangement products according to *Chemical Abstracts*, which lists the compounds as derivatives of benzanilide or benzamide. Since the Chapman rearrangement is used as a preparative method for diarylamines, we have stressed this fact by calling the initial products aroyldiarylamines, providing a uniform nomenclature. Similarly, we have named all the compounds obtained by amide hydrolysis as diarylamines, even though *Chemical Abstracts* often uses other names. For example, 3 is named 2'-chlorodiphenylamine-2-carboxylic acid rather



than *N*-(*o*-chlorophenyl)anthranilic acid. Acridones are numbered according to *Chemical Abstracts*.

MECHANISM

The Chapman rearrangement has been shown to be an intramolecular reaction in which a 1,3 shift of an aryl group from oxygen to nitrogen occurs. The reaction, which proceeds via a 4-membered transition state, may be considered as a nucleophilic attack by nitrogen on the migrating aryl group.

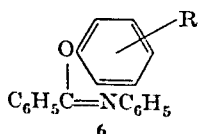


Wiberg and Rowland showed that the reaction is intramolecular by heating a mixture of phenyl *N*-phenylbenzimidate (4, *R* = *R*' = H) and

p-chlorophenyl *N*-(*p*-chlorophenyl)benzimidate (4, $R = R' = \text{Cl}$).⁹ The infrared spectra and x-ray powder patterns of the reaction mixtures showed that the composition was the same as those obtained when the two imidates were heated separately and the products mixed. Earlier, Chapman had performed a similar experiment with a mixture of 4 ($R = R' = \text{H}$) and 4 ($R = R' = \text{CH}_3$). The absence of the mixed product 5 ($R = \text{H}, R' = \text{CH}_3$) in the pyrolysis product, which was determined only from the freezing point of the mixture, led Chapman to conclude correctly that the reaction is intramolecular.²

Chapman² also used freezing point data to determine that the rearrangement of phenyl *N*-phenylbenzimidate followed first-order kinetics. In a later paper, however, in which a large number of imidates were pyrolyzed, he determined the percentages of the unreacted basic imidates in the mixtures by titration with acid.³ Since his rate data were obtained using molten imidates (no solvent), the results were probably not very accurate. Wiberg and Rowland conducted kinetic experiments on a variety of imidates in diphenyl ether, under carefully controlled conditions, and confirmed Chapman's conclusion that the reaction is unimolecular.⁹

Chapman studied the rates of rearrangement of several imidates 6, which differed only in the substituents on the aryloxy ring.³ By far the most reactive was 6 ($R = o\text{-NO}_2$) since over 40% was rearranged in 90 minutes at 162–163°. The next most reactive compound, 6 ($R = 2,4,6\text{-Cl}_3$), was unchanged at this temperature, but 87% conversion to the amide occurred when it was heated for 90 minutes at 200–201°. The



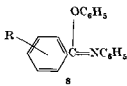
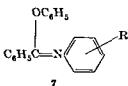
parent compound 6 ($R = \text{H}$) required a temperature of 266° for 90 minutes to effect 74% conversion to amide. The least reactive compound studied, 6 ($R = p\text{-CH}_3\text{O}$) required 90 minutes at 266° for 44% rearrangement.

Chapman concluded that the rate of the reaction was associated with the acidity of the phenol from which the imidate was derived and that the rearrangement proceeded via a four-membered intermediate. He believed that the aryl group migrated with the pair of electrons bound to oxygen. The first suggestion that the reaction is initiated by nucleophilic attack of the unshared electrons of the nitrogen atom was made in *Annual Reports*.¹⁰ Later Wiberg and Rowland⁹ concluded from their kinetic

study that the reaction is indeed essentially a nucleophilic displacement on an aromatic ring. Electron-attracting groups on the aryloxy ring accelerate the reaction by helping to accommodate the partial negative charge induced on the ring by the nitrogen electrons. Alkyl imidates do not undergo the normal Chapman rearrangement (see p. 26) presumably because the saturated alkyl group, in contrast to an aryl group, cannot accommodate the additional negative charge.

Wiberg and Rowland studied a larger number of imidates, **6**, where R is an *ortho* or a *para* substituent. In all but one case, the *ortho*-substituted compound reacted more rapidly than the *para*, confirming Chapman's earlier observations. Wiberg attributed this to an entropy effect; the *ortho* group lessened the entropy decrease in going from the reactant to the four-membered transition state. The one exception involved the *o*-*t*-butyl group, where steric compressibility is important. For a fuller explanation of the entropy effects, as well as a discussion of the geometric configurations of the imidates, the original paper should be consulted.⁹ In a later paper Wiberg discussed the various types of reactions in which intramolecular 1,3 shifts take place.¹¹

Chapman also studied several imidates which differed only in the substituents on the arylimino ring.³ He found that compound **7** (R = *p*-CH₃O) rearranged faster than compound **7** (R = H). The imide **7** (R = 2,4,6-Cl₃) was considerably less reactive than the parent compound. Thus electron-withdrawing groups make the electrons on nitrogen less available for nucleophilic attack and slow down the reaction. Derivatives of the imide **8** exhibited the same behavior, but the effect

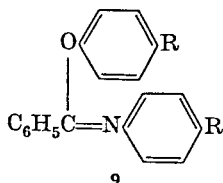


was less marked.³ Compound **7** (R = *o*-NO₂) could not be rearranged successfully even at 220°; above this temperature decomposition occurred.³ Owing to resonance, the electrons of arylamines are less available than those of alkylamines, and it would seem reasonable that N-alkyl imidates would rearrange readily. However, in the only case reported, the N-methyl analog of **7** decomposed without isomerizing.³

The imide **6** (R = *p*-Br) rearranged more rapidly than the corresponding *p*-chloro compound, which in turn rearranged more rapidly than

¹¹ Wiberg and Shryne, *J. Am. Chem. Soc.*, **77**, 2774 (1955).

the parent imidate **9** ($R = H$).⁹ The parent imidate **9** ($R = H$) was



converted to N-benzoyldiphenylamine in 80% yield by heating for 1 hour at 280°. ¹² The dibromo analog **9** ($R = Br$) required heating for 2 hours to effect a comparable conversion. It therefore appears that in this case the effect of the substituent in the nitrogen-bonded ring is greater than that in the oxygen-bonded ring. A more dramatic effect is reported for the difluoro compound **9** ($R = F$), heating for 18 hours at 280° being required for 80% conversion. ¹² This is attributed to the great electron-withdrawing ability of fluorine, the halide atom in the nitrogen-bonded ring again being the dominant factor. Kinetic data on a variety of compounds substituted in the nitrogen-bonded ring alone and in both rings would be of great interest for determining the relative effects of substituents in the two rings. Both monofluoro imidates **6** ($R = p-F$) and **7** ($R = p-F$) have been converted in over 80% yield to the amides upon heating at 305–310° for 1 hour. ¹³ However, no kinetic data are available. Rate data on the imidate **6** ($R = p-F$) would be of special interest since a *p*-fluorine atom may either accelerate or decelerate (relative to *p*-H) nucleophilic displacement. ¹⁴

SCOPE AND LIMITATIONS

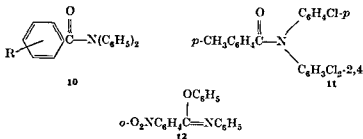
The objective of the early work on the pyrolysis of aryl imidates was to obtain information about the mechanism of the reaction, rather than to develop it for preparative purposes. ^{1–3} In 1929 it was pointed out that the rearrangement could serve as a general method for preparing diphenylamines by hydrolysis of the primary reaction products, ⁴ and a variety of substituted diarylamines has since been prepared in this way. The Chapman rearrangement has been carried out successfully with most of the imidates tried, and yields have generally been high. Unfortunately, yields have not been reported for many reactions, especially those reported in the earlier literature. The conversion of phenyl N-phenylbenzimidate to N-benzoyldiphenylamine was said to be complete after 2 hours at 270–300° and no by-products were formed, but the yield of crystallized product was not reported. ² Similarly it has been implied that various chloro-substituted imidates rearranged quantitatively, but yields were not given. ³

¹² Benington, Shoop, and Pairier, *J. Org. Chem.*, **18**, 1506 (1953).

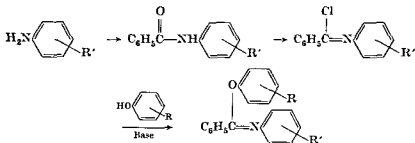
¹³ Schulenberg and Archer, unpublished results.

¹⁴ Bauer and Huisgen, *Angew. Chem.*, **72**, 399 (1960).

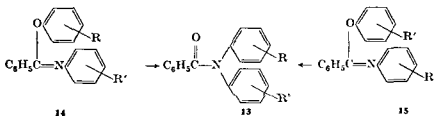
The reaction can be used also to prepare aroyldiphenylamines substituted in the aroyl ring, e.g., the compounds **10** where R is *o*-chloro, *p*-chloro, *p*-nitro, *p*-methoxy, and 2,4,6-trichloro,³ and the even more highly substituted aroylamine **11**.¹⁵ An attempt to rearrange **12** was unsuccessful.³



The usefulness of the Chapman rearrangement obviously depends on the availability of the aryl imidates, which are generally prepared by the following route.



For the preparation of unsymmetrically substituted diarylamines **13**, either of two imidates, **14** or **15**, may be utilized. The choice between



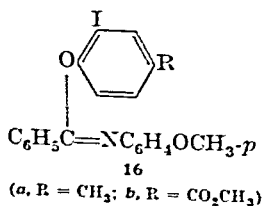
14 and **15** is often dictated by the relative availabilities of the amine and the phenolic components. When both sets of reagents are available, the imidate selected is usually the one which will rearrange at the lower temperature. Therefore the more acidic phenol (with electron-withdrawing substituents) should be chosen.⁴ In several cases, both imidates have

¹⁵ Jamison and Turner, *J. Chem. Soc.*, 1937, 1954.

been used successfully. For example, all six possible monochloroimidates have been prepared and pyrolyzed to the three isomeric N-benzoylchlorodiphenylamines.^{2,3} On the other hand, while the imidate 14 ($R = o\text{-NO}_2$, $R' = \text{H}$), was converted in 40 % yield to N-benzoyl-*o*-nitrodiphenylamine in 1 hour at 165°, the isomeric compound 14 ($R = \text{H}$, $R' = o\text{-NO}_2$) did not rearrange.³

A great variety of halogenated diarylamines has been prepared by the Chapman rearrangement: the monochlorodiphenylamines previously mentioned and a large number of dichloro-, trichloro- and tetrachlorodiphenylamines.^{3,4,15-20} The pentachloro imidate 14 ($R = 2,4,6\text{-Cl}_3$, $R' = 2,4\text{-Cl}_2$) was converted to the N-benzoyldiarylamine in 81 % yield, and this product was then hydrolyzed to 2,2',4,4',6-pentachlorodiphenylamine in 92 % yield.¹⁵ The hexachloro compound 14 ($R = R' = 2,4,6\text{-Cl}_3$) has also been rearranged successfully.³

N-Benzoyl-2,2'-dibromodiphenylamine²¹ and its 4,4'-dibromo analog²² have been prepared and hydrolyzed to the diphenylamines. In the former case the rearranged product was obtained in 86 % yield, and its hydrolysis product in 87 % yield. The iodine-containing imidates 16a and 16b were rearranged to the N-benzoyldiphenylamines in 56 % and 95 % yields, respectively.²³

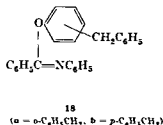
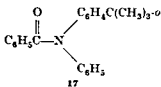


Pyrolysis of the fluorine-containing imidate, 14 ($R = R' = p\text{-F}$), has been reported to furnish N-benzoyl-4,4'-difluorodiphenylamine (80 % yield) which was hydrolyzed almost quantitatively to 4,4'-difluorodiphenylamine.¹²

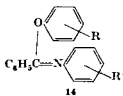
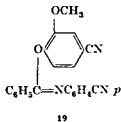
The first alkyl-substituted aryl imidate to be pyrolyzed was the dimethyl derivative 14 ($R = R' = p\text{-CH}_3$) which was converted to N-benzoyl-4,4'-dimethyldiphenylamine.² A little later the synthesis of several monomethyl- and dimethyl-diphenylamines via the Chapman route was

reported^{24,25} Two of these, 3-methyldiphenylamine²⁴ and 2,3'-dimethyldiphenylamine,²⁵ were each prepared via both isomeric imidates. 4-Methyldiphenylamine was synthesized in an overall yield of 84 % based on the imide 14 ($R = H$, $R' = p\text{-CH}_3$).²⁶

Wiberg and Rowland prepared and rearranged two ethyl-substituted imidates, 14 ($R = o\text{-C}_2\text{H}_5$, $R' = H$) and 14 ($R = p\text{-C}_2\text{H}_5$, $R' = H$), and the corresponding isopropyl compounds but did not isolate any of the four alkylbenzoyldiphenylamines.⁹ The same workers pyrolyzed a large number of imidates for their kinetic study, but the only product isolated was the *t*-butyl compound 17 (40 % yield).⁹ *N*-Benzoyl-4,4'-di-*t*-butyldiphenylamine was reported much earlier as resulting in "almost quantitative" yield by heating the corresponding imide at 300°.²⁷ Benzyl groups are stable at the temperature required for the Chapman rearrangement. Both benzylphenyl imidates 18 were converted to the desired aroyldiphenylamines in over 80 % yield by heating at 275°.²⁸



In addition to alkyl- and halogen-substituted imidates, compounds bearing methoxy, nitro, acetyl, benzoyl, cyano, and carbalkoxy groups have been rearranged. The three isomers of 14 ($R' = H$, $R = \text{OCH}_3$), as well as 14 ($R = H$, $R' = p\text{-OCH}_3$), were converted to *N*-benzoyldiphenylamines.³ Since then, the iodo-methoxy imidates²³ 16 and the dicyanomethoxy imide²⁹ 19 have been rearranged.



²⁴ Gibson and Johnson, *J. Chem. Soc.*, 1929, 1473.

²⁵ Gibson and Johnson, *J. Chem. Soc.*, 1929, 2743.

²⁶ Hey and Moynahan, *J. Chem. Soc.*, 1959, 1563.

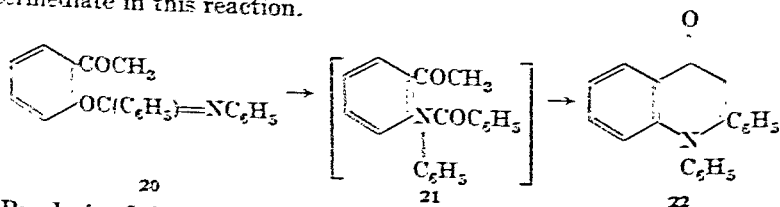
²⁷ Craig, *J. Am. Chem. Soc.*, 57, 195 (1935).

²⁸ Waters and Watson, *J. Chem. Soc.*, 1957, 253.

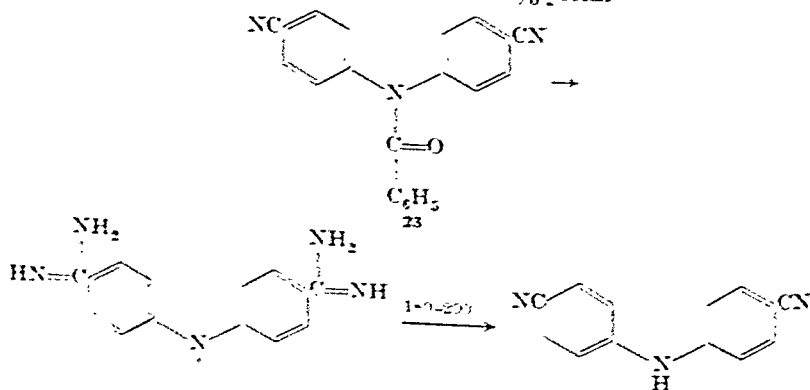
²⁹ Easson, *J. Chem. Soc.*, 1961, 1029.

Compounds 14 ($R = o\text{-NO}_2$, $R' = \text{H}^2$ and $R = o\text{-NO}_2$, $R' = 2\text{-Br}$, 4-CH_3^{20}) were converted to the desired benzyldiarylamines by heating for 1 hour at less than 200° , but under similar treatment 14 ($R = p\text{-NO}_2$, $R' = \text{H}$ and $R = \text{H}$, $R' = o\text{-NO}_2$) decomposed to tarry materials.³ No *m*-nitro compounds have been studied.

Only three acyl-substituted imidates have been subjected to pyrolysis. The *para*-substituted compounds 14 ($R = p\text{-CH}_3\text{CO}$, $R' = \text{H}^2$ and $R = p\text{-C}_6\text{H}_5\text{CO}$, $R' = \text{H}^{21}$) reacted normally. The latter gave *N*,4-dibenzoyldiphenylamine (90% yield), which on hydrolysis lost the *N*-benzoyl group and furnished the diarylamine in 89% yield. The *o*-acetyl compound 20 when pyrolyzed at 267° gave the quinoline derivative 22.² The normal Chapman rearrangement product, 21, was an intermediate in this reaction.

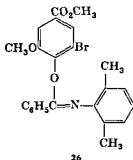


Pyrolysis of the appropriate imidate at $280\text{--}300^\circ$ furnished *N*-benzoyl-4,4'-dicyanodiphenylamine (23).²² Hydrolysis with sodium hydroxide in ethylene glycol afforded 4,4'-dicyanodiphenylamine (25). Ammonolysis of the nitrile 23 gave the diamidino compound 24 which, when heated, gave benzamide and the diarylamine 25 in 76% yield.

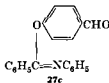
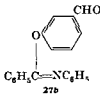
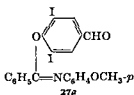


Several derivatives of the dinitrile **23** substituted in the *ortho* positions have been prepared by the Chapman rearrangement in high yield.²⁹ For example, the imidate **14** ($R = 2\text{-Cl}$, 4-CN , $R' = p\text{-CN}$) heated in boiling Dowtherm furnished the *o*-chloro analog of **23** in 84% yield. Hydrolysis in ethylene glycol gave 2-chloro-4,4'-dicyanodiphenylamine in 60% yield. The 2-methoxy compounds, analogs of **23** and **25**, were similarly prepared in yields of 88% and 86%, respectively. The imidate **14** ($R = 2\text{-NO}_2$, 4-CN , $R' = p\text{-CN}$) was quantitatively rearranged in either boiling anisole or pyridine, but the product could not be hydrolyzed cleanly to 4,4'-dicyano-2-nitrodiphenylamine. The last-named compound was synthesized by nitration of the dicyanodiphenylamine **25**.²⁹ Only two cyano-containing imidates, **14** ($R = p\text{-CN}$, $R' = 2\text{-NO}_2$, 4-CN and $R = R' = 2\text{-NO}_2$, 4-CN), that could not be rearranged to the appropriate diphenylamine have been reported.²⁹

The conversion of **14** ($R = p\text{-CO}_2\text{CH}_3$, $R' = \text{H}$) to *N*-benzoyl-4-carbomethoxydiphenylamine in high yield has been reported by two groups of investigators.^{26,33} Hydrolysis to diphenylamine-4-carboxylic acid proceeded smoothly in 73% yield.²⁶ Attempts to isomerize the *meta*-substituted ester analog (**14**, $R = m\text{-CO}_2\text{CH}_3$, $R' = \text{H}$),³³ the corresponding carboxylic acid,³³ or the ester **26** failed.³⁴ The rearrangement of derivatives of salicylic acid is discussed on pp. 13-15.



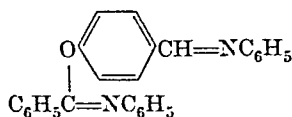
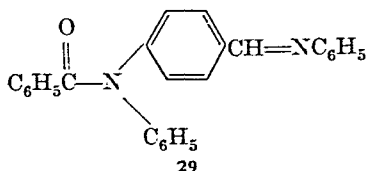
The imidates **27** containing aldehyde groups could not be rearranged.^{23,33} However, the anil **28** pyrolyzed at 270° to furnish presumably the expected



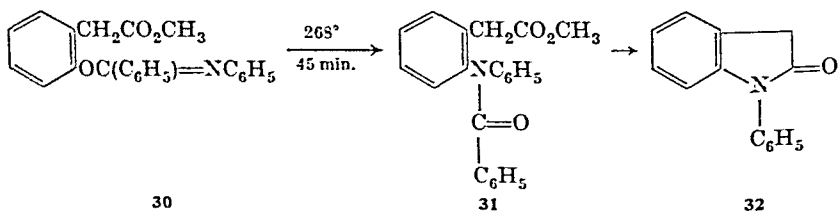
²⁹ Brown, Carter, and Tomlinson, *J. Chem. Soc.*, 1958, 1843.

³⁴ Harris, Potter, and Turner, *J. Chem. Soc.*, 1955, 145.

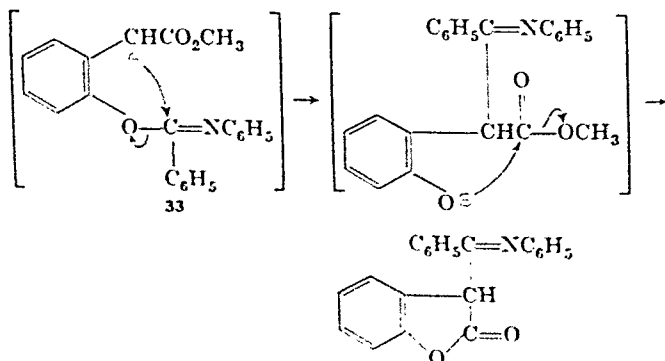
rearrangement product **29**, which, however, could not be hydrolyzed to N-benzoyldiphenylamine-4-carboxaldehyde.³³

**28****29**

Only one abnormal Chapman rearrangement has been reported, excluding those examples where the normal product results and then reacts further.³⁵ The carbomethoxymethyl derivative **30** on pyrolysis gave a mixture from which two products, each obtained in 29% yield, were identified. One was shown to be the normal rearrangement product **31**; hydrolysis with base followed by acidification gave the expected N-phenyl-oxindole (**32**).

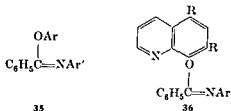
**30****31****32**

The other product was 3-benzanilimino-2(3*H*)benzofuranone (**34**). The following mechanism involving basic catalysis (imidates are weakly basic) and rearrangement of the anion **33** was proposed.³⁵ The imideate **30** on



treatment with sodium methoxide in boiling benzene furnished the furanone **34** in 56% yield, showing the feasibility of the proposed base-catalyzed reaction.³⁵ Other imidates with active hydrogen atoms on the *ortho* substituent could also be expected to give abnormal pyrolysis products. In these cases the isomeric imidates should be used to prepare the desired aroyldiphenylamines.

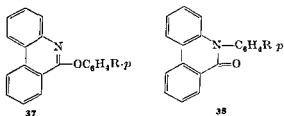
Relatively few imidates containing aryl groups other than phenyl or substituted phenyl groups have been rearranged. Chapman pyrolyzed the three naphthyl derivatives **35**. The first two gave *N*-benzoyl-*N*-phenyl- α -naphthylamine; the third gave the corresponding β -naphthylamine.³



- (a, Ar = C₆H₅, Ar' = α -C₁₀H₇) (d, R = H, Ar = C₆H₅)
 (b, Ar = α -C₁₀H₇, Ar' = C₆H₅) (e, R = H, Ar = *o*-CH₃C₆H₄)
 (c, Ar = β -C₁₀H₇, Ar' = C₆H₅) (f, R = Cl, Ar = C₆H₅)
 (d, R = H, Ar = *o*-ClC₆H₄)
 (e, R = H, Ar = 2-Br-4-CH₃C₆H₃)
 (f, R = H, Ar = 2-Br-4, 6-(CH₃)₂C₆H₃)

Hall pyrolyzed the six 8-quinolinylnyl imidates **36**; the first in 72% yield, the second and third in unspecified yield, and the remaining three unsuccessfully.³⁰

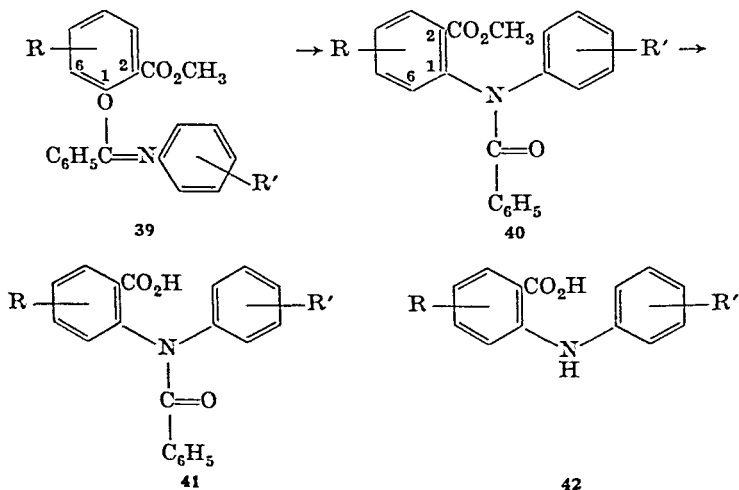
Hey and Moynahan rearranged three imidates **37** derived from phenanthridine;²⁶ the phenoxy derivative (R = H) to the phenanthridone **38** in 60% yield, the analogs (R = Cl) and (R = CH₃) in 75% and 70% yields, respectively.



Diphenylamine-2-carboxylic Acids

The Chapman rearrangement of imidates in which the phenolic component is a salicylic acid derivative serves as a synthesis of derivatives

of diphenylamine-2-carboxylic acid (N-phenylanthranilic acid). The development of this synthesis is due to Jamison and Turner who showed that the parent imidate **39** ($R = R' = H$), prepared from methyl salicylate and N-phenylbenzimidoyl chloride, rearranged readily to the aroylamine **40** in 73% yield on heating for 10 minutes at 270–275°. Hydrolysis of the aroylamine with 1 mole of base gave the N-benzoyl acid **41** in 76% yield, and excess base gave diphenylamine-2-carboxylic acid (**42**) in 96% yield.¹⁵ (In a later paper the yield was reported as 78%.³⁶)

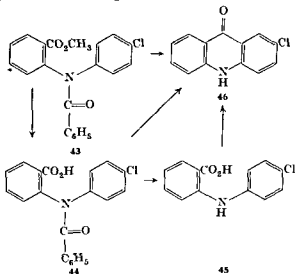


The rearrangement of a variety of substituted imidates also proceeded well, usually in better than 80% yield. Among these were chloro, bromo, methoxy, and methyl analogs of **39**.¹⁵ Later a large number of imidates derived from 3-methylsalicylic acid were rearranged, for example, the imidates **39** in which $R = 6-CH_3$ and $R' = H, o-F, o-Cl, o-Br$, and $o-CH_3$.^{34,36,37} The rearrangement products were all partially hydrolyzed to the corresponding N-benzoyl acids **41**,^{15,34,36-39} many of which were partially or completely resolved and their optical stabilities studied.^{34,37-39} The only imidate that could not be isomerized to the desired aroyldiphenylamine was **39** in which $R = 6-CH_3$ and $R' = 2,4,6-(CH_3)_3$.³⁴

The imidate **30** derived from *o*-hydroxyphenylacetic acid gave a mixture of a benzofuranone and the normal rearrangement product on pyrolysis. (See p. 12.) However, the compounds **39** ($R = H$, $R' = o\text{-CH}_2\text{CO}_2\text{CH}_3$ or $o\text{-CH}_2\text{CO}_2\text{C}_2\text{H}_5$), containing a carbalkoxymethyl substituent in the phenyl group bonded to nitrogen, rearranged normally in 83% and 91% yield, respectively.⁴⁴

Acridones

Jamison and Turner were also the first to use the products of the Chapman rearrangement as intermediates for the synthesis of acridones¹⁵ 2-Chloroacridone (**46**) was prepared by them in three different ways. The aroylamine **43**, (which had been prepared by heating the appropriate imidate at 270°) was pyrolyzed at 320°, yielding methyl benzoate and the acridone **46**. The yield was "not quantitative." The second route involved partial hydrolysis to the acid **44** which was heated for 5 minutes at 250°. Benzoic acid was eliminated and the acridone **46** obtained in 90% yield. The third path utilized the completely hydrolyzed acid **45** which was converted to **46** by treatment with phosphorus oxychloride and hydrolysis of the resulting 2,9-dichloroacridine,⁴⁵ the over-all yield was 87%.¹⁵



⁴⁰ G. Singh, S. Singh, A. Singh, and M. Singh, *J. Indian Chem. Soc.*, **29**, 781 (1952).

⁴¹ G. Singh, A. Singh, S. Singh, and M. Singh, *J. Indian Chem. Soc.*, **28**, 698 (1951).

⁴² G. Singh, S. Singh, A. Singh, and M. Singh, *J. Indian Chem. Soc.*, **28**, 459 (1951).

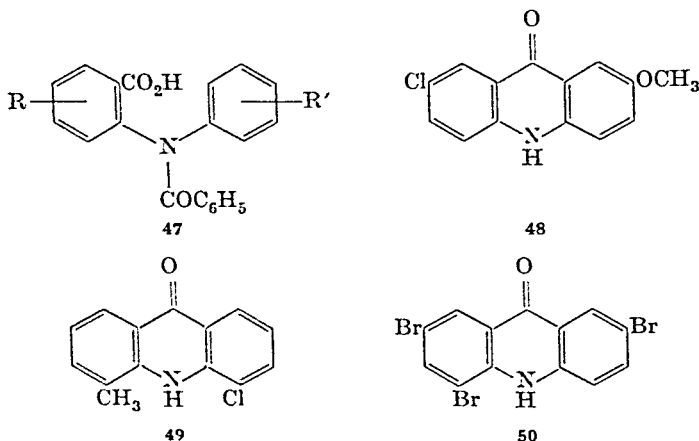
⁴³ S. Singh, *J. Sci. Ind. Res. (India)*, **10B**, 82-6 (1951) [*C.A.*, **46**, 2547 (1952)].

⁴⁴ Schulenberg and Archer, *J. Am. Chem. Soc.*, **83**, 3091 (1961).

⁴⁵ N. S. Drozdov and S. S. Drozdov, *J. Gen. Chem. USSR (Engl. Transl.)*, **4**, 1 (1934) [*C.A.*, **28**, 5456 (1934)]; N. S. Drozdov, *ibid.*, **4**, 117 (1934) [*C.A.*, **28**, 5456 (1934)].

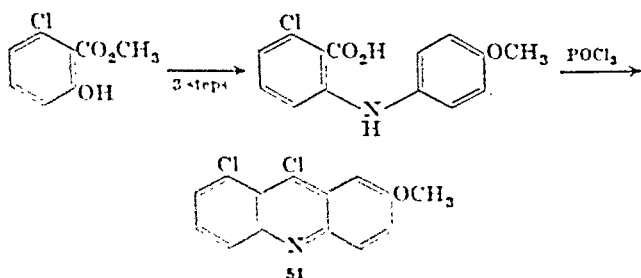
Surprisingly, the parent compound 47 ($R = R' = H$) did not give acridone at temperatures as high as 350° .¹⁵ On the other hand, the acid 47 ($R = H$, $R' = 2,4(CH_3)_2$) formed 2,4-dimethylacridone in 71% yield when it was pyrolyzed at 300° for a few minutes, but the corresponding ester did not give the acridone when heated at 350° .¹⁵

Pyrolysis of compounds 47 ($R = 4-Cl$, $R' = p-OCH_3$) and 47 ($R = 6-CH_3$, $R' = o-Cl$) gave, respectively, the acridones 48, in almost quantitative yield,¹⁵ and 49 in 86% yield.³⁶ The phosphorus oxychloride method was used for the preparation of the acridone 50 in 91% yield.¹⁵

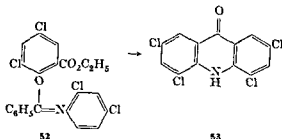


2-Chloro-6-methoxyacridone was prepared in unspecified yields by all three routes.⁴² The isomeric 5-chloro-3-methoxyacridone was prepared by the two pyrolytic methods,⁴⁰ while an acridone, believed to be the 1-chloro-6-methoxy isomer, was synthesized by the phosphorus oxychloride route.⁴¹ 2-Iodo-6-methoxyacridone was also synthesized by pyrolysis of the ester and by the phosphorus oxychloride method.⁴³ In all cases the starting imide was that derived from 4-methoxysalicylic acid.⁴⁰⁻⁴³

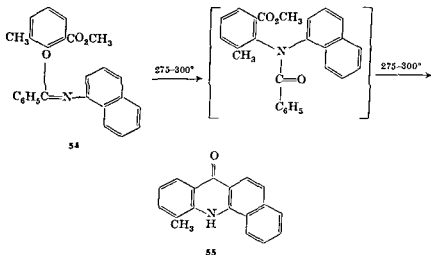
1,9-Dichloro-7-methoxyacridine (51) was prepared as shown in the



accompanying formulation.⁴⁶ The over-all yield was 28% based on methyl 6-chlorosalicylate. Ionescu synthesized 2,4,5,7-tetrachloroacridone (53) in 10% yield by heating the imide 52 for 10 minutes at 260° and, without isolating the product, heating for 1 minute at 200° with concentrated sulfuric acid.⁴⁷



The synthesis of acridones with additional fused rings, using the Chapman rearrangement, was first accomplished by Cymerman-Craig and Loder.⁴⁸ They pyrolyzed the imide 54 which rearranged and lost methyl benzoate to form the benzacridone 55 in 72% yield. The intermediate benzoxydiarylamine was not obtained.

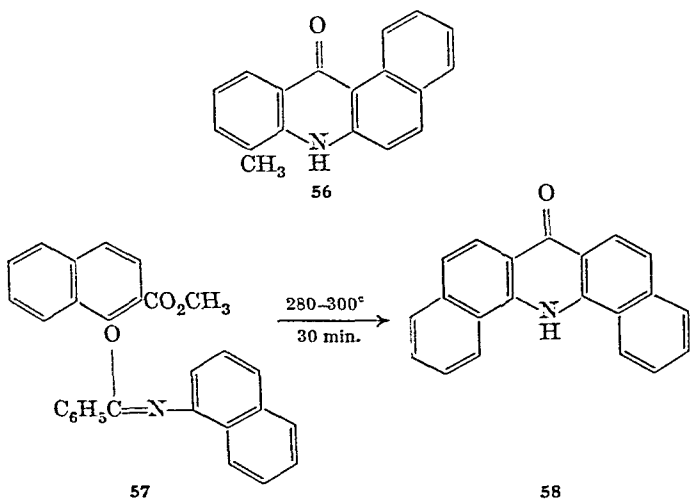


Similarly the β -naphthyl analog of 54 gave the acridone 56 in 38% yield on pyrolysis for 30 minutes at 360°, and the imide 57 gave the pentaacyclic acridone 58 in 47% yield on pyrolysis.⁴⁸

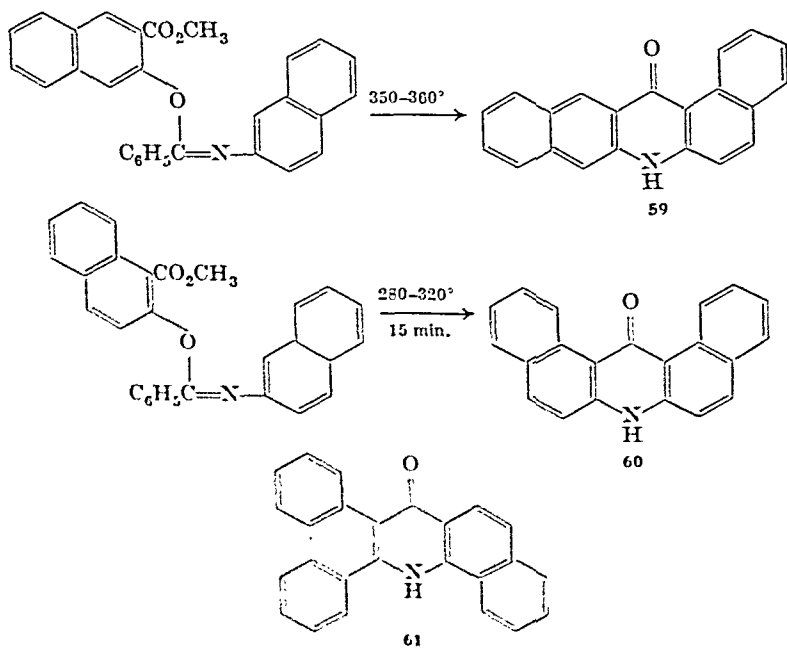
⁴⁶ Dauben and Hodgson, *J. Am. Chem. Soc.*, **72**, 3479 (1950)

⁴⁷ Ionescu, Goia, and Felmeri, *Acad. Rep. Populare Romine, Filiala Cluj, Studii Cercetari Chem.*, **8**, 351 (1957) [*C.A.*, **54**, 4587 (1960)], Ionescu and Goia, *Rev. Chim. Acad. Rep. Populare Roumaine*, **5**, No. 1, 85 (1960) [*C.A.*, **55**, 9402 (1961)]

⁴⁸ Cymerman-Craig and Loder, *J. Chem. Soc.*, 1955, 4309

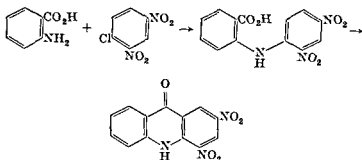


Two other pentacyclic acridones, 59⁴⁸ and 60,⁴⁹ were synthesized in 54% and 80% yield, respectively, as indicated in the equations, but an attempt to prepare the hexacyclic acridone 61 failed.⁴⁸

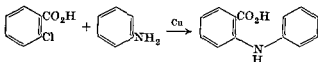


COMPARISON WITH OTHER METHODS

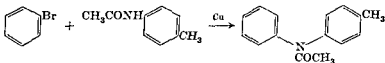
The majority of substituted diphenylamines reported in the literature has been prepared by direct nucleophilic displacement of halide by aromatic amines. The uncatalyzed reaction, discovered by Jourdan,



proceeds only with highly activated halides such as 2,4-dinitrochlorobenzene.^{49,50} The copper-catalyzed reaction, known as the Ullmann condensation,^{49,51,52}



is of much greater general utility.^{50,53,54} This reaction has been applied chiefly to the synthesis of diphenylamines substituted with nitro or carboxyl groups. If diphenylamines that do not contain nitro or carboxyl groups are desired, a two-step procedure may be used: an Ullmann reaction between aniline or a substituted aniline and an o-chlorobenzoic acid, followed by thermal decarboxylation of the product. The Goldberg diphenylamine synthesis,



⁴⁹ Albert, *The Acridines*, E. Arnold and Co., London, 1951, p. 42.

⁵⁰ Surrey, *Name Reactions in Organic Chemistry*, Academic Press, New York, 1961, p. 236.

⁵¹ Ullmann, *Ber.*, 36, 2382 (1903).

⁵² Bunnett and Zahler, *Chem. Rev.*, 49, 392 (1951).

⁵⁴ Acheson, *Acridines*, Interscience Division, John Wiley and Sons, New York, 1956, p. 148; (a) p. 157; (b) p. 105.

the reaction of *N*-acylanilines with aryl halides followed by hydrolysis, is a copper-catalyzed reaction also.^{8c,55-57}

The Chapman synthesis involves five steps from the starting aniline: benzanilide formation, conversion to imidoyl chloride, imidate synthesis, rearrangement, and hydrolysis. All five steps are easily carried out and two of the intermediates, the imidoyl chloride and the rearrangement product, are often not isolated. However, the Ullmann synthesis will generally require less time and, if other factors are equal, is to be preferred.

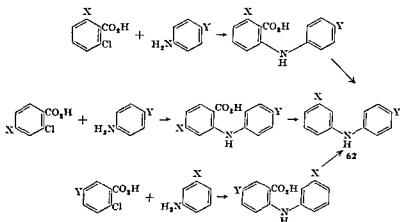
It is difficult to compare the yields by these two routes since, for most of the examples of the Chapman method, yields are not given in all steps. This is especially true in the early literature where the preparation of most of the simpler diphenylamines is reported. Furthermore, many of the *N*-benzoyldiphenylamines were not hydrolyzed. Although a huge number of derivatives of diphenylamine-2-carboxylic acid has been prepared by the Ullmann condensation, only a small percentage has been decarboxylated; most have been converted to acridine derivatives.^{50,54} Some of the yields reported in the early literature are questionable. Ullmann reported that *o*-toluidine and *o*-chlorobenzoic acid could be converted to 2-methyldiphenylamine in an over-all yield of 87% (the decarboxylation was claimed to be quantitative).⁵³ In a recent paper an over-all yield of 33% was reported.⁵⁹ The corresponding *o*-chloro and *o*-methoxy compounds were obtained in 69% and 52% over-all yields, respectively.⁵⁹ The corresponding yields via the Chapman synthesis are not available.

Yields are reported for imidate formation,^{9,24} rearrangement,²⁴ and hydrolysis²⁴ in the preparation of 3-methyldiphenylamine. When the higher yield reported for the imidate synthesis is used,⁹ an over-all yield of 35% can be estimated. Ullmann reported a 62% yield in the reaction between *o*-chlorobenzoic acid and *m*-toluidine, but no yield was given for the decarboxylation.⁵³ Ullmann claimed that the corresponding 4-methyl acid, obtained in 89% yield from *p*-toluidine, was decarboxylated quantitatively.⁵³ 4-Methyldiphenylamine was synthesized from phenol and benz-*p*-toluidide by the Chapman route in 74% over-all yield.²⁵

A large number of chloro-substituted diphenylamines was prepared by Elson and Gibson by Ullmann condensation of *o*-chlorobenzoic acid and various aniline derivatives.¹⁹ The products from 2,5-dichloroaniline and 3,4-dichloroaniline were decarboxylated in 85% and 75% yields, respectively, but no yields were reported for the condensation reaction.¹⁹

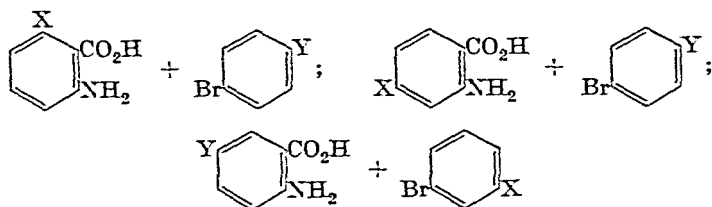
Over-all yields (three steps) for several dihalodiphenylamines prepared by the Chapman route are very similar. 4,4'-Difluorodiphenylamine was synthesized in 48% yield,¹² the corresponding 4,4'-dibromo compound was obtained in 43% yield,²² and the dichloro analog was prepared in 47% yield.¹⁵ Good over-all yields were obtained for the following more highly substituted compounds: 2,4,4'-trichlorodiphenylamine, 62%;¹⁵ 2-methyl-4,4'-dicyanodiphenylamine, 61%;²⁹ and 2,2',4,4',6-pentachlorodiphenylamine, 66%.¹⁵ Although direct comparison of the two methods is not possible, it seems evident that at least comparable yields are attainable by the longer route.

Frequently the choice between the two methods will depend on availability of starting materials. Often the needed *o*-chlorobenzoic acid will be difficult to obtain, whereas the corresponding phenol will be available. In this case the Chapman route will obviously be preferred. It must be kept in mind that there are always *at least* two sets of reagents leading to a diphenylamine via the Ullmann condensation and decarboxylation. To illustrate, the diarylamine 62 can be prepared in the following ways

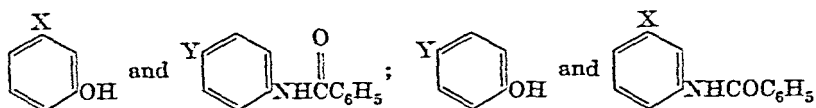


If Y were a *meta* or *ortho* substituent, a fourth possibility would exist. Furthermore, anthranilic acids will react with derivatives of bromobenzene to give diphenylamine-2-carboxylic acids.⁶⁰ Although chloro compounds are generally unreactive and bromo compounds must be used, the method has the advantage that some substituted anthranilic acids are commercially available while the corresponding *o*-chloro acids are not.⁵⁰ Therefore the following three sets of reagents must also be considered for the synthesis of 62.

⁶⁰ Goldberg, *Ber.*, 39, 1691 (1906).



For the Chapman synthesis only two sets of compounds must be considered.



The Goldberg synthesis appears to be the preferred method for some of the simpler compounds. When *p*-chloroacetanilide and bromobenzene were treated with copper, potassium iodide, and iodine and the resulting product was hydrolyzed, 4-chlorodiphenylamine resulted in 72% yield.⁶¹ Earlier, Goldberg⁵⁵ reported the conversion of *m*-nitroacetanilide and bromobenzene to 3-nitrodiphenylamine in 80% yield. Weston and Adkins studied thoroughly the reaction between acet-*p*-toluidide and bromobenzene, determining the effects of changes in catalyst and solvent.⁵⁷ Davis and Ashdown synthesized a large number of nitrodiphenylamines by the Goldberg procedure but gave no yields.⁵⁶ They also reported, without yields, the synthesis of nitrodiphenylamines from the unacetylated nitroanilines.⁵⁶ Earlier Goldberg had reported the direct conversion of *o*-nitroaniline and bromobenzene to 2-nitrodiphenylamine in 75–80% yield.⁵⁵

The Ullmann condensation suffers some drawbacks, a major one being that reductive dehalogenation may sometimes become the major reaction.⁵³ Limitations of the reaction are discussed by Acheson.⁵⁴²

When the appropriate *o*-chlorobenzoic acid is readily available, the Ullmann route will generally be preferred for the preparation of diphenylamine-2-carboxylic acids and the acridones derived from them. The parent acid itself has been prepared in 82–93% yield by the Ullmann procedure (one step).⁶² while the three-step Chapman method from methyl salicylate and *N*-phenylbenzimidoyl chloride gave an over-all yield of 57%.¹⁵ In a later paper lower yields were reported for the same Chapman route.³⁶ However, 4'-chlorodiphenylamine-2-carboxylic acid was prepared in about 75% over-all yield using the Chapman rearrangement, so the two methods may give comparable yields in some cases.¹⁵ If the

necessary *o*-chloro acid is not available, the Chapman rearrangement may well be preferable since it proceeds particularly well with derivatives of methyl salicylate.^{15,34,36,37}

Some Chapman rearrangement products can be converted directly to acridones by heating, but this does not appear to be a general reaction.¹⁵ When the thermal reaction is possible, acridones may be synthesized in two steps from derivatives of methyl salicylate, so this route may in some cases be the preferred one, particularly in the synthesis of acridones with additional fused rings.⁴³ For example, 1,2,7,8-dibenzoacridone (60) (p. 18) was prepared by this method in 80% yield from the imide after the Ullmann condensation between β -naphthylamine and 2-chloro-1-naphthoic acid was found to give only 1–2% of the desired diarylamine.⁴⁹

In addition to the Ullmann and Chapman routes, a few other methods for synthesizing diphenylamines may be mentioned. Some compounds may be prepared by substitution of diphenylamine, e.g., 4,4'-dibromodiphenylamine by direct bromination.⁶³ This compound has also been prepared via the Chapman rearrangement.²² Certain symmetrical compounds may be prepared by the reaction of equimolar amounts of an amine and its hydrochloride. Diphenylamine itself is best prepared in this way from aniline and aniline hydrochloride.^{7a} Occasionally, unsymmetrical amines are also prepared by this method, but the mixed product must be separated from the three-component mixture that is obtained.^{7a}

Diphenylamines may also be prepared by the reaction between an amine and a phenol.^{7b} The parent compound has been synthesized by heating aniline and phenol at 250° with antimony trichloride as the catalyst.⁶⁴ The reaction between nitrobenzene and phenylmagnesium bromide is reported to give diphenylamine in 58% yield.⁶⁵ Similarly, methyl *p*-nitrobenzoate and phenylmagnesium bromide gave 4-carbomethoxydiphenylamine in 45% yield.⁶⁶ In contrast, the Ullmann condensation between iodobenzene and methyl *p*-aminobenzoate gave the same product in only 27% yield.⁶⁷ The corresponding acid has also been synthesized in 46% yield via the Chapman route starting with methyl *p*-hydroxybenzoate and *N*-phenylbenzimidoyl chloride.²⁵

Finally, one example should be cited in which the Chapman method gave a good yield of the desired amine after several other routes failed completely. Jones and Mann²¹ were unable to synthesize 2,2'-dibromodiphenylamine from *o*-chloronitrobenzene and *o*-bromoaniline, from

⁶³ Galatis and Megaloukonomos, *Prakt. Akad. Athenon*, 9, 20 (1934) [*Chem. Zentr.*, 105, 11, 2974 (1934)].

⁶⁴ Buch, *Ber.*, 17, 2634 (1884).

⁶⁵ Gilman and McCracken, *J. Am. Chem. Soc.*, 51, 821 (1929).

⁶⁶ Curtin and Kauer, *J. Am. Chem. Soc.*, 75, 6041 (1953).

⁶⁷ Gilman and Brown, *J. Am. Chem. Soc.*, 62, 3208 (1940).

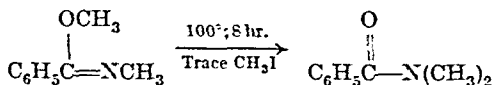
o-bromoaniline and its hydrochloride, from *o*-bromophenol and *o*-bromoaniline (with a zinc chloride catalyst), or from *o*-chloronitrobenzene and the sodium salt of *o*-bromoacetanilide. The Chapman route gave the desired product in 36% over-all yield.²¹

RELATED REACTIONS

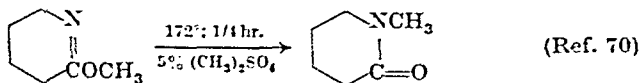
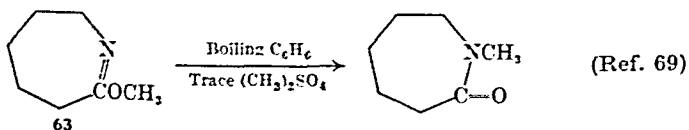
There are several imidate-amide rearrangements which present many features of interest but which do not have the usefulness of the Chapman rearrangement. In this section these related reactions are discussed, but completeness of coverage is not attempted.

Catalyzed Rearrangements of Alkyl Imidates

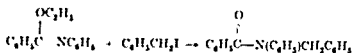
The conversion of alkyl imidates to amides has been reported by many investigators, but the first careful study was that of Lander who found that the reaction proceeds well when catalyzed by small amounts of an alkyl halide. The rearrangement shown in the accompanying equation is typical of many others described by Lander.⁶⁸



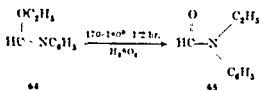
Dialkyl sulfates have been used as catalysts for the conversion of *O*-alkyl lactams to *N*-alkyl lactams.



When *O*-ethyl caprolactim (the ethyl homolog of 63) was heated with dimethyl sulfate, a mixture of the *N*-methyl and *N*-ethyl lactams resulted.⁷⁰ Acyclic analogs gave similar results.⁶⁹ In contrast to the Chapman reaction, the Lander rearrangement is intermolecular. Arbuzov has recently made use of the intermolecular nature of the reaction by treating alkyl imidates with various halides.⁷¹ The following reaction has been carried out in 90% yield.⁷¹



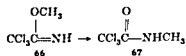
Roberts and Vogt studied the rearrangement of alkyl imidates in the presence of sulfuric acid. The accompanying reaction was carried out in 41-53% yield.⁷² The reaction proceeded in better yield (74-85%)



when a half mole of triethyl orthoformate was present in the reaction mixture. The *p*-chloro analog of 64 was rearranged in 63% yield without the use of additional orthoformate while the *O*-methyl analog gave *N*-methylformanilide in 61% yield.⁷² Treatment of 64 with sulfuric acid and triisooamyl orthoformate furnished a mixture of the *N*-ethyl (65) and *N*-isooamyl amides.⁷² Thus it is clear that the reaction is intermolecular and analogous to the Lander rearrangement. Presumably, the sulfuric acid generates an alkylating species from the ortho ester (and from the imidate) which is equivalent to the alkyl halide catalyst used by Lander.

Since ethyl *N*-phenylformimidate (64) is prepared from aniline and triethyl orthoformate by an acid-catalyzed reaction and rearranged to *N*-ethylformanilide (65) in the presence of acids, it is possible to prepare the anilide 65 from aniline and triethyl orthoformate in a single step without isolating the imidate. The anilide 65 is readily hydrolyzed to *N*-ethylaniline in high yield. Roberts has suggested these reactions as a practical synthesis of the monoalkylanilines.⁷²

Cramer and Hennrich studied the rearrangement of trichloroacetimidates and found that boron trifluoride is an excellent catalyst for the reaction.⁷³ The methyl ester 66 gave the amide 67 in 91% yield, while the corresponding ethyl ester rearranged in 96% yield. The benzyl ester

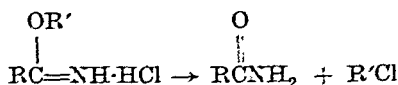


gave only 15% of *N*-benzyltrichloroacetamide, the remainder being trichloroacetamide.⁷³

⁷² Roberts and Vogt, *J. Am. Chem. Soc.*, **78**, 4778 (1956).

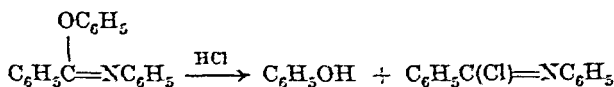
⁷³ Cramer and Hennrich, *Chem. Ber.*, **94**, 976 (1961).

Although boron trifluoride and sulfuric acid can be used to catalyze the rearrangements of imidates, acids which furnish good nucleophiles cannot. When imidate hydrochlorides are heated, cleavage occurs instead of rearrangement. This reaction, known as the Pinner fission,



has been studied by McElvain⁷⁴ and Cramer.⁷⁵ It involves nucleophilic attack by chloride ion on the protonated imidate.

Aryl imidates do not undergo the Pinner fission. Phenyl *N*-phenylbenzimidate on heating with hydrogen chloride yielded phenol and *N*-phenylbenzimidoyl chloride.⁷⁶



Thermal Rearrangement of Alkyl Imidates

There have been several reports of the thermal isomerization of alkyl imidates, but, except for the methyl, benzyl, and allyl derivatives which will be considered later, when the reactions were re-examined it was found that the pure imidates did not rearrange. Two examples will suffice.

The imidate 68 was reported to rearrange to the amide 69 in 35% yield on heating for 6 hours at 270–280°.⁷⁷ Lander, in the first careful study of the thermal behavior of alkyl imidates, showed that the carefully purified imidate 68 underwent negligible isomerization after 8 hours at 250–270° and 3 hours at 300°.⁶⁵ Similarly the imidate 70 was reported to

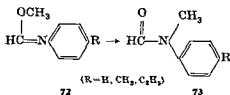


rearrange to the lactam 71 in 85% yield after 2 hours at 180–250°.⁶⁹ Later it was shown that the rearrangement of 70 was due to the presence of an impurity, probably diethyl sulfate.⁷⁹



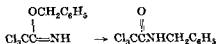
When the alkyl group in an alkyl imidate can undergo elimination, this, rather than isomerization, appears to be the normal pyrolysis pattern. Thus the ethyl and *sec*-butyl analogs of 68 furnished benzanilide and ethylene⁶⁸ and 2-butene,⁹ respectively, and the imidate 70 yielded caprolactam and ethylene.⁷⁰ Pyrolysis of alkyl imidates has been suggested as a way of dehydrating secondary alcohols.⁹

Since elimination cannot occur, pyrolysis of methyl imidates can apparently give rearrangement products; e.g., the methyl imidate 68 gave the amide 69 in 25% yield when heated at 300–330°,³ and conversion of 72 to the amides 73 occurred in 20–40% yields at about 300°. ⁷⁸



The temperatures needed are higher than those generally required for the Chapman rearrangement of aryl imidates, and the yields are lower. The reaction has been shown to be intermolecular, in contrast to the Chapman rearrangement which is intramolecular.⁷⁸ Wiberg⁹ believes that the thermal rearrangement of alkyl imidates is a free radical process.

Benzyl imidates, like the methyl compounds, cannot undergo the elimination reaction and would be expected to rearrange. The thermal conversion shown in the accompanying equation has been reported without reference to reaction conditions.⁷⁹



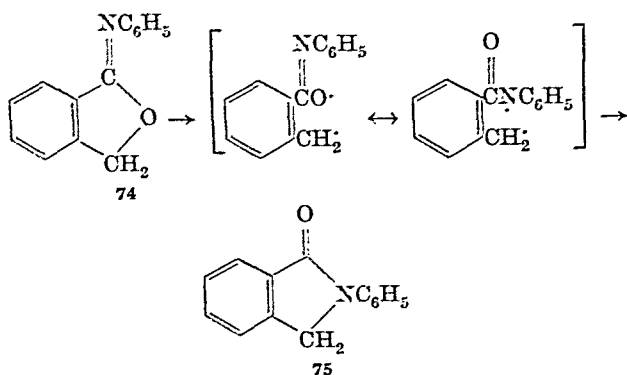
The cyclic benzyl imidate 74 furnished the isoindole derivative 75 in 70% yield when heated for 2 hours at 300°. ⁸⁰ On steric grounds the four-membered transition state of the Chapman rearrangement cannot exist,

⁷⁸ Wiberg, Shryne, and Kintner, *J. Am. Chem. Soc.*, **79**, 3160 (1957).

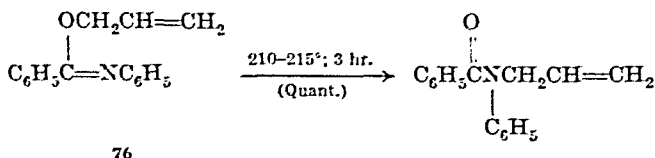
⁷⁹ Cramer, Pawelzik, and Kupper, *Angew. Chem.*, **68**, 649 (1956).

⁸⁰ Stirling, *J. Chem. Soc.*, 1960, 235.

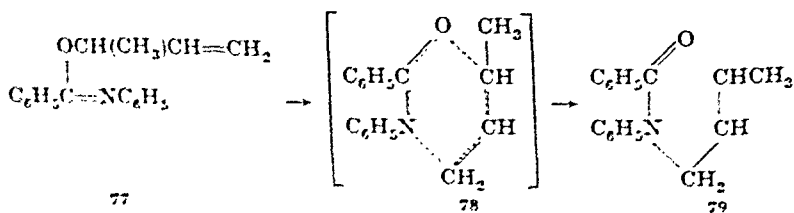
and it seems likely that the reaction proceeds via the intermediate diradical shown in the formulation. Attempts to rearrange the analogous N-benzyl and N-cyclohexyl compounds at 300° failed.⁸⁰



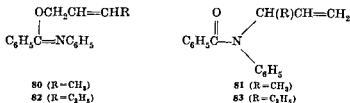
Allyl imidates undergo thermal rearrangement more readily than the methyl or benzyl derivatives. The reaction was first observed by Mumm and Möller⁸¹ with the allyl imidate 76.



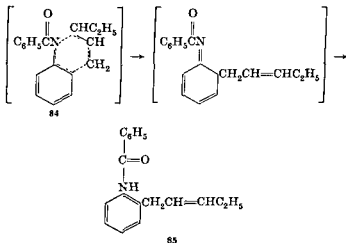
This rearrangement could conceivably occur either via a four-membered or a six-membered transition state. Mumm showed that the latter was the route indicating that the reaction resembles the Claisen rather than the Chapman rearrangement. The imidate 77 gave the amide 79 stereospecifically, presumably via 78.⁸¹



Similarly, the imidate 80 yielded the amide 81.⁸¹ If the Chapman mechanism had been operative, the expected product would be 79.



The higher homolog 82 rearranged at 235° to furnish 83.⁸² When either 82 or 83 was heated for 3 hours at 290°, a different product, 85, was obtained.⁸² Evidently this resulted via a six-membered transition state 84 strictly analogous to that postulated for the Claisen rearrangement.



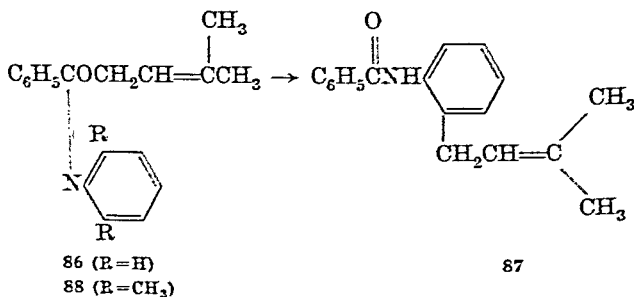
Earlier the rearrangement of the terminally substituted imidate 86 at 225–260° was shown to result in a 75% conversion to 87. The possible intermediate 89 (corresponding to 83) was not obtained.⁸³

⁸¹ Lauer and Benton, *J. Org. Chem.*, **24**, 804 (1959).

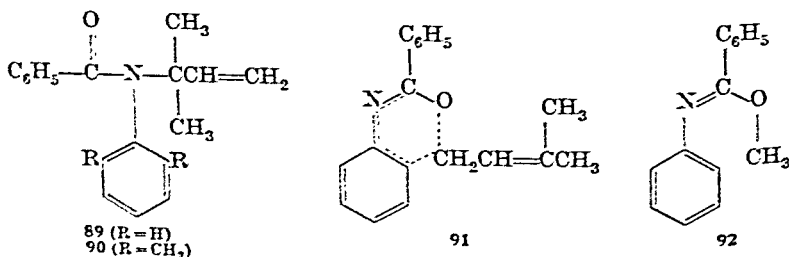
* Recently the conversion of N-allyl-1-naphthylamine to 2-allyl-1-naphthylamine was claimed to be the first example of a Claisen rearrangement from a nitrogen atom.⁸² Apparently the earlier work was overlooked.

⁸² Marcinkiewicz, Green, and Mamalis, *Tetrahedron*, **14**, 208 (1961).

⁸³ Lauer and Lockwood, *J. Am. Chem. Soc.*, **76**, 3974 (1954).

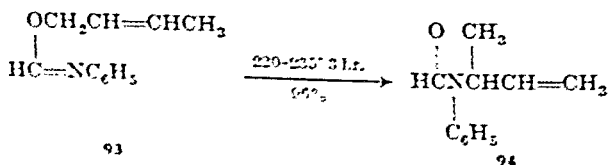


The analogous *o,o'*-disubstituted imidate 88, which could not lead to aryl substitution, gave only benz-2,6-dimethylanilide on pyrolysis; 90 was not obtained.⁸² Lauer therefore concluded that the rearrangement of 86 to 87 is probably not a two-step reaction and does not proceed via 89. Instead, a one-step mechanism proceeding via the transition state 91 was postulated.^{82,84} However, the steric effect exerted by the two *ortho* methyl groups in 88 could conceivably prevent formation of 90 even if 89 were formed normally. Furthermore, it seems unlikely that 86



would rearrange readily via 91 at 260° since the imidate 92 is stable at 300°.⁸⁵ The mechanism of this change is doubtful at present.

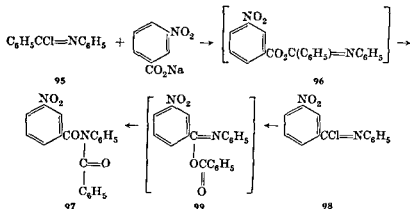
Although the preceding thermal reactions proceed stereospecifically and intramolecularly, the acid-catalyzed rearrangement of allyl imidates gives mixtures, undoubtedly by way of an ionic mechanism. Roberts and Hussein found that the thermal rearrangement of the imidate 93, for example, gave 94.⁸⁵ In contrast, when the same imidate, 93, was heated



with concentrated sulfuric acid, reaction began at 100° and a mixture of many components, including 94 and its allylic isomer, resulted.⁸⁵

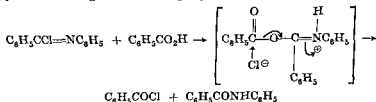
Rearrangements of Acyl Imidates

The Mumm rearrangement, which apparently involves the rearrangement of acyl imidates (imino anhydrides), was discovered before the Chapman rearrangement. When N-phenylbenzimidoyl chloride (95) was treated with sodium *m*-nitrobenzoate, the expected product 96 was not isolated; instead, the diacylaniline 97 was obtained.¹ N-Phenyl-*m*-



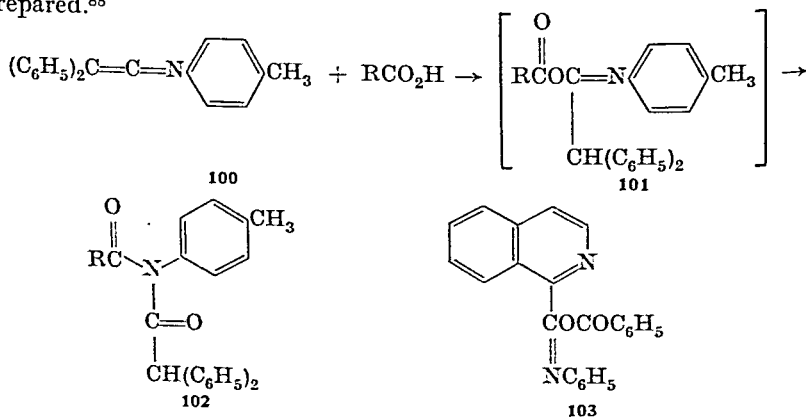
nitrobenzimidoyl chloride 98 and sodium benzoate also gave 97, presumably via the acyl imidate 99.¹ In no case could an O-acyl compound be isolated. As a result of this failure Mumm was led to study the behavior of a stable aryl imidate and, as a result, discovered the reaction now known as the Chapman rearrangement.

Recently Cramer and Baer attempted to prepare acyl imidates from the reaction of imidoyl chlorides, carboxylic acids, and triethylamine.⁸⁶ As before, no intermediates could be isolated; the imides were obtained in almost quantitative yield. When the triethylamine was omitted, a reaction analogous to the Pinner fission resulted, and acyl halides and amides were isolated. For example, benzoyl chloride was obtained in 90% yield according to the accompanying formulation.⁸⁵



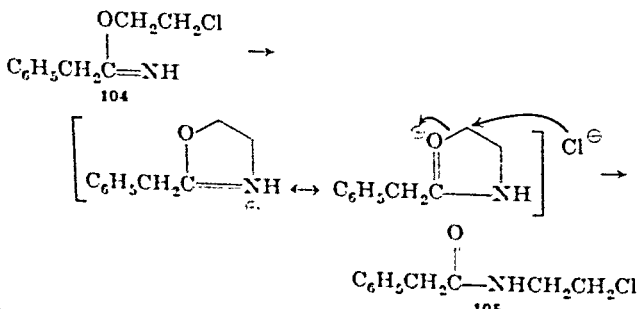
²⁴ Cramer and Baer, *Chem. Rev.*, **93**, 1231 (1960).

Stevens and Munk⁸⁷ prepared imides (102) from diphenylketene *p*-tolylimine (100) and carboxylic acids, but the anticipated acyl imidates (101) were not isolated. The authors suggested that the reaction proceeded via a four-membered transition state; if so, it is mechanistically analogous to the Chapman rearrangement. The same authors also briefly mention other related reactions which involve acyl migration from oxygen to nitrogen, probably via four-membered transition states.⁸⁷ Recently a compound believed to be a stable acyl imidate (103) has been prepared.⁸⁸

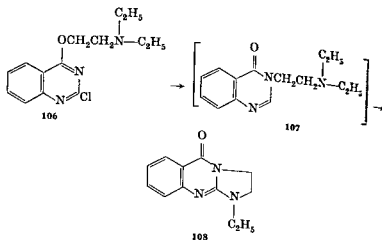


Miscellaneous Rearrangements

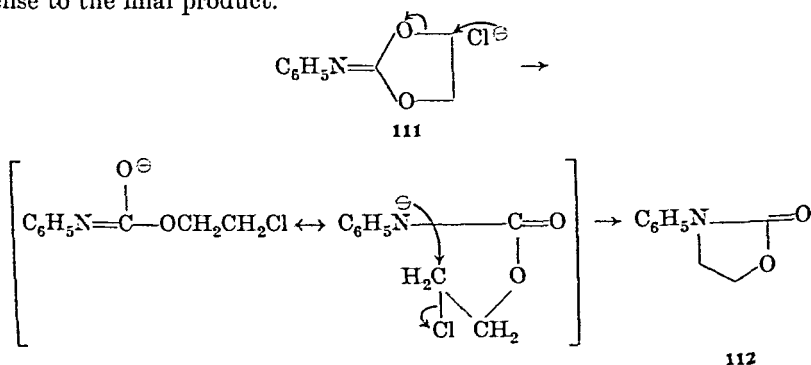
The conversion of the chloroethyl imidate 104 to the amide 105 takes place at 130°.⁸⁹ The low temperature indicates that neither the normal Chapman rearrangement nor a dissociation into radicals occurs. Most likely the reaction proceeds via internal displacement of halogen to give the five-membered intermediate shown. Nucleophilic attack of chloride ion would then give the amide.



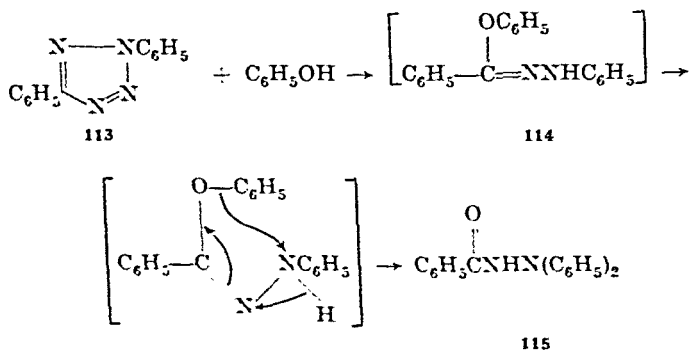
The quinazoline **106** is converted to the tricyclic compound **108** upon distillation at 211° .⁹⁰ It has been suggested that the reaction proceeds by way of **107**. The mechanism for the formation of **107** is uncertain. A route analogous to that suggested for the rearrangement of **104** seems unlikely, since this would involve formation of an ion pair containing the diethylamide anion.



The cyclic imine **111** has been converted to the urethan **112** by heating with lithium chloride.⁹² The reaction probably proceeds by halide ion attack to give the intermediate shown, which then closes in the alternative sense to the final product.

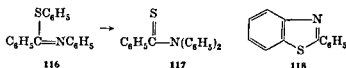


The tetrazole **113** is converted to the hydrazide **115** in refluxing phenol.⁹³ The reaction presumably proceeded through the intermediacy of **114** which, Huisgen suggested, rearranges via a five-membered cyclic transition state. This route, which would involve a hydride shift, supposedly took precedence over the Chapman rearrangement because of the larger ring involved in the transition state.⁹³

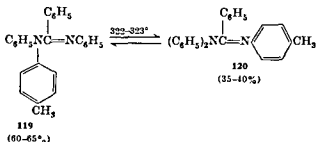


As a natural extension of his study of aryl imidates, Chapman examined sulfur analogs such as **116**. At 280–290° for 2 hours, isomerization to **117** took place only to a small extent. At 320°, both **116** and **117** gave a mixture containing diphenyl sulfide, benzonitrile, thiophenol, and the

benzthiazole 118. Since both reactants gave the same mixture, Chapman suggested that the rearrangement is reversible.⁹⁴



In a series of papers Chapman reported on the analogous amidines.^{16-18,95,96} Here, as expected, the rearrangement was shown to be reversible. Either 119 or 120 on heating gave the equilibrium mixture shown in the equation.⁹⁵



Chapman also heated a mixture of triphenylbenzamidine and tri-*p*-tolylbenzamidine. Since the mixture after heating had the same melting point as before, it was concluded that no mixed amidines had been formed and that the reaction is intramolecular.¹⁶ The mechanism is probably completely analogous to that of the Chapman imidate rearrangement. In the amidine rearrangement, if all three N-aryl groups are different, an equilibrium mixture of three components should result, but, if the three aryl groups are identical, aryl migration leads only to starting material.

Chapman³ believed that the thermal rearrangement of aryl imidates was reversible, but, since heating aroyldiphenylamines failed to produce detectable amounts of imidates, he concluded that the equilibrium lies so far to the amide side that reversibility is not appreciable. No examples of the reverse reaction have been reported thus far.

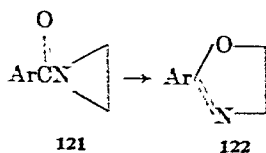
The thermal rearrangement of aroylaziridines such as 121 to cyclic imidates 122 has been reported. Since this reaction is readily catalyzed

⁹⁴ Chapman, *J. Chem. Soc.*, 1926, 2296.

⁹⁵ Chapman, *J. Chem. Soc.*, 1929, 2133.

⁹⁶ Chapman and Perrott, *J. Chem. Soc.*, 1930, 2462.

by acids or nucleophiles (iodide ion), it is uncertain whether the uncatalyzed reaction really occurs.⁹⁷



EXPERIMENTAL CONDITIONS

N-Arylbenzimidoyl Chlorides

The conversion of amides to imidoyl chlorides has generally been carried out by heating with an equimolecular amount of phosphorus pentachloride, usually without solvent.^{93,99} The reaction often begins spontaneously at room temperature, and, after removal of the resulting phosphorus oxychloride, the product may be isolated either by crystallization or distillation, the latter being preferred for low-melting solids. Frequently, after removal of the phosphorus oxychloride, the crude product is used directly without purification.^{12,29,25,44} Occasionally, carbon tetrachloride²⁹ or toluene¹⁰⁰ has been used as a solvent for the reaction.

Thionyl chloride has been used less frequently but has given equally good results,^{52,101,102} as exemplified by the preparation of N-phenylbenzimidoyl chloride in 95% or better yield.^{52,101} Phosphorus oxychloride has been used for the preparation of N-(9-phenanthryl)benzimidoyl chloride, but no yield was given.⁴⁵ The authors of this chapter have found this reagent distinctly inferior to phosphorus pentachloride or thionyl chloride in the preparation of N-(4-fluorophenyl)benzimidoyl chloride.¹³

Aryl N-Arylbenzimidates

Phenyl N-phenylbenzimidate was first prepared by Hantzsch from a suspension of sodium phenoxide and N-phenylbenzimidoyl chloride in ether.¹⁰³ Since then, almost all imidates have been synthesized by treating the phenol with sodium ethoxide in ethanol and then adding

the imidoyl chloride in ether.^{9,15,104} The reaction, which is often run under nitrogen, takes place readily at room temperature. The imidates are usually crystalline and are easily isolated, generally in high yield. Commercial sodium methoxide in methanol gives equally good results.^{35,44} A slight excess of the phenol is often used.

Dioxane²³ and ethyl acetate¹³ may be used instead of ether for dissolving the chlorides. Cookson has also prepared imidates from phenols and imidoyl chlorides in pyridine, the last reagent serving both as base and solvent.²³ Easson has treated sodium salts of cyanophenols in pyridine with either the molten imidoyl chloride or the chloride in pyridine.²⁹ Good results were also obtained from phenols, chlorides, and triethylamine in ether or dioxane.²⁹

N-Aroyldiarylamines

The Chapman rearrangement has usually been carried out by heating the imidate without a solvent. In most cases, temperatures of 250–300° are used. However, imidates derived from acidic phenols will rearrange at lower temperatures, *o*-nitrophenyl *N*-phenylbenzimidate being converted to *N*-benzoyl-*o*-nitrodiphenylamine in 1 hour at 165°.³ Usually heating periods of less than 3 hours are sufficient. Imidates derived from methyl salicylate are usually rearranged by heating at about 280° for about 10 minutes.¹⁵ The reaction is exothermic and the internal temperature may go above 300° if a large quantity of imidate is pyrolyzed. In experiments where temperature control is not critical, the vessel used for the rearrangement may be heated by a Wood's metal bath. If more careful control is desired, a constant external temperature may be held by heating the vessel with the vapors of a high-boiling material such as bibenzyl.³⁵

In a few reactions, solvents have been used. Cookson was unable to obtain crystalline rearrangement products by heating certain iodine-containing imidates without solvent. However, when nitrobenzene (b.p. 209°), diphenyl ether (b.p. 259°), biphenyl (b.p. 254°), or *o*-dichlorobenzene (b.p. 180°) was used as solvent, the desired product could be obtained in reasonable yield in some cases.²³ Dowtherm was used successfully as the solvent for rearranging many cyanoimidates.²⁹ Imidates derived from *o*-nitrophenol have been rearranged in boiling anisole (b.p. 155°) and even pyridine (115°).²⁹ In Wiberg's⁹ kinetic study of the Chapman rearrangement, diphenyl ether was used as the solvent.

¹⁰⁴ Chapman, *J. Chem. Soc.*, 121, 1676 (1922).

Hydrolysis of Rearrangement Products

Hydrolysis of the rearrangement products was first carried out by Chapman who heated under reflux a mixture of 10 g. of *N*-benzoyldiarylamine, 50 ml. of 50% aqueous potassium hydroxide, and 125 ml. of ethanol for 2 hours.⁴ Essentially the same method of basic hydrolysis has been used in almost all cases reported, the only changes being in the relative proportions of reagents. Sodium hydroxide in aqueous ethylene glycol has been employed to hydrolyze a series of cyano-substituted *N*-benzoylamines.²⁹

Hydrolysis of the rearrangement products derived from methyl salicylate to derivatives of diphenylamine-2-carboxylic acids is also carried out with excess base in aqueous ethanol¹⁵ or aqueous dioxane.⁴⁴ Essentially the same procedure, but with equimolar amounts of alkali and *N*-benzoyl ester, is used for the partial hydrolysis of these compounds to the *N*-benzoyl acids.¹⁵

Acridones

Although acridones have been prepared directly from benzimidates and from derivatives of *N*-benzoyldiphenylamine-2-carboxylic acid, very few examples have been reported. Because detailed experimental directions have rarely been given, little can be said about experimental conditions. For the preparation of acridones via other routes, the reader should consult Acheson.^{54b}

at 110–116°/0.15 mm., through a short Vigreux column. Rapid distillation is necessary to prevent the yellow distillate from crystallizing in the apparatus. The yield is 41.6 g. (98%) of almost white solid, m.p. 58–63°.

Phosphorus Pentachloride. (a) A mixture of 10.8 g. (0.05 mole) of 4'-fluorobenzanilide and 10.4 g. (0.05 mole) of phosphorus pentachloride is heated under reflux for 1 hour. After removal of the phosphorus oxychloride at water pump vacuum, the product is distilled using an oil pump to give 10.6 g. (91%) of product.

(b) The phosphorus oxychloride is removed as described above, and the residue is crystallized from hexane to give 9.3 g. (79%) of white solid. The product is less pure than the distilled material and gives a cloudy melt. Recrystallization from hexane gives the product, m.p. 62–65°, in 54% yield.

o-Carbomethoxyphenyl *N*-Phenylbenzimidate.^{15,36} A 250-ml. three-necked flask, equipped with a Hershberg stirrer and a delivery tube arranged so that a slow stream of nitrogen passes through the liquid, is charged with 100 ml. of absolute ethanol to which is added 1.9 g. (0.083 g. atom) of sodium. After the conversion to sodium ethoxide is complete, the solution is cooled to room temperature and a solution of 15.2 g. (0.10 mole) of methyl salicylate in 15 ml. of absolute ethanol is added quickly. A solution of 17.3 g. (0.08 mole) of *N*-phenylbenzimidoyl chloride in 30 ml. of dry diethyl ether is then added within a few minutes. The reaction mixture is stirred overnight at room temperature under nitrogen, most of the solvent is removed in vacuum, and the residue is mixed with water. The insoluble solid is recrystallized from absolute ethanol to give 23.5 g. (89%) of white prisms, m.p. 114–117°. Ultraviolet (ethanol): λ_{\max} 227 m μ (ϵ 27,345) and 275 m μ (ϵ 11,720). Infrared (KBr): 5.82 μ , 6.00 μ .

p-Fluorophenyl *N*-(*p*-Fluorophenyl)benzimidate.¹² In a 250-ml. flask equipped with a magnetic stirrer, 6.5 g. (0.12 mole) of sodium methoxide (Matheson, Coleman and Bell) is dissolved in 125 ml. of methanol and the solution is cooled to about 20°. Then 13.4 g. (0.12 mole) of *p*-fluorophenol (Aldrich) is added all at once. In the course of the next few minutes a solution of 23.4 g. (0.10 mole) of *N*-(*p*-fluorophenyl)benzimidoyl chloride in 50 ml. of dry ethyl acetate is added. The mixture turns cloudy at once, and the temperature rises from 25° to 37°.

The mixture is stirred for 3 hours, after which time the solvent is removed in vacuum. Water is added and the white insoluble solid filtered and washed with water. After air-drying, 27 g. (m.p. 99–106°) of the product is obtained which upon recrystallization from absolute ethanol gives 23.5 g. (83%) of material which melts at 105–109°. Ultraviolet

(ethanol): λ_{\max} 220 $m\mu$ (shoulder, ϵ 16,300), 229 $m\mu$ (shoulder, ϵ 15,500), 266 $m\mu$ (ϵ 6560), and 272 $m\mu$ (ϵ 6500). Infrared (KBr): 6.08 μ .

***o*-Carbomethoxyphenyl N-[(*o*-Carbomethoxymethyl)phenyl]-benzimidate.**⁴⁴ N[(*o*-Carbomethoxymethyl)phenyl]benzimidoyl chloride is prepared by mixing 56.5 g. (0.21 mole) of methyl *o*-benzamido phenyl-acetate⁴⁴ and 43.7 g. (0.21 mole) of phosphorus pentachloride in a 500-ml. flask. The reaction begins spontaneously at room temperature, and hydrogen chloride evolution occurs with extensive foaming. The mixture is then heated gently on the steam bath until the gas evolution virtually ceases. The phosphorus oxychloride is removed in vacuum below 50°, toluene is added, and the solvent once again removed in vacuum to leave the crude imidoyl chloride as a dark red oil, which is used without purification.

Meanwhile a solution of 12.4 g. (0.23 mole) of sodium methoxide in 200 ml. of methanol is flushed with nitrogen and cooled with an ice bath. To this is added with stirring a solution of 35.0 g. (0.23 mole) of methyl salicylate in 50 ml. of methanol. The crude imidoyl chloride in 65 ml. of anhydrous diethyl ether is then added during 5 minutes. The ice bath is removed and the cloudy tan mixture stirred for 3 hours at room temperature, after which water is added and the product taken up in ether. The red extracts are dried and the solvent is removed to give a dark oil which solidifies and is crystallized from methanol-hexane to furnish 59.2 g. (70%) of yellow prisms, m.p. 60–64°. This material is pure enough to be used directly in the Chapman rearrangement. Two recrystallizations from methanol give a white solid, m.p. 62–65°. Ultraviolet (ethanol): λ_{\max} 228 $m\mu$ (ϵ 24,000), 278 $m\mu$ (ϵ 5400). Infrared (KBr): 5.80 μ and 5.97 μ .

N-Benzoyldiphenylamine.^{2,12} Five grams of phenyl N-phenylbenzimidate is placed in a small pear-shaped flask carrying a thermometer that dips into the solid. The flask is immersed for an hour in a Wood's metal bath held at 312–315°. The melt, whose temperature during the heating is 305–310°, crystallizes on cooling. The solid is taken up in warm absolute ethanol. After cooling, filtering, washing the tan solid with ethanol and air-drying, 4.6 g. (92%) of product, m.p. 177–181° is obtained. One recrystallization from absolute ethanol (charcoal) gives 4.0 g. (80%) of white needles, m.p. 178–182°. Ultraviolet (ethanol): λ_{\max} 235 $m\mu$ (shoulder ϵ 13,100), 271 $m\mu$ (ϵ 7220). Infrared (KBr): 6.09 μ .

Methyl N-Benzoyldiphenylamine-2-carboxylate.^{15,36} A 125-ml. Erlenmeyer flask equipped with a thermometer and containing 30 g. of *o*-carbomethoxyphenyl N-phenylbenzimidate is heated in a Wood's metal bath. When the bath temperature reaches 240°, an exothermic reaction begins and the internal temperature quickly rises to 260°. After about

a minute, the internal temperature begins to drop. The bath is then heated for 10 minutes at 280°. The dark melt is cooled somewhat, then poured into 160 ml. of hot absolute ethanol. On cooling, the product crystallizes to give 24.5 g. (82%) of slightly yellow solid, m.p. 133–135.5°. Ultraviolet (ethanol): inflection at 273 m μ , ϵ 6830. Infrared (KBr): 5.80 μ , 6.04 μ .

Methyl 2,6-Diiodo-4'-methoxydiphenylamine-4-carboxylate.²³ A solution of 4.0 g. of 4-carbomethoxy-2,6-diiodophenyl-N-p-methoxyphenylbenzimidate²³ in 12 ml. of *o*-dichlorobenzene is heated under reflux for 80 minutes. Petroleum ether (b.p. 100–120°) is added until crystals begin to separate from the boiling solution. On cooling, 3.8 g. (95%) of the product is obtained. After recrystallization from toluene-petroleum ether (b.p. 100–120°), the pure material melts at 205°.

4-Fluorodiphenylamine.¹³ A mixture of 10.9 g. (0.037 mole) of N-benzoyl-4-fluorodiphenylamine, 30 g. of potassium hydroxide in 30 ml. of water, and 125 ml. of ethanol is heated under reflux for 2 hours. Water is added and the mixture is concentrated in vacuum in order to remove most of the ethanol. The cloudy mixture is then extracted three times with diethyl ether and the extracts dried. Removal of the solvent gives a dark red oil which is vacuum-distilled with a small Vigreux column. The product is obtained as a yellow liquid, b.p. 78–80°/0.01 mm., which crystallizes on cooling, m.p. 33.5–35.5°; yield 5.9 g. (85%). Ultraviolet (ethanol): λ_{\max} 241 m μ (shoulder ϵ 3860), 281 m μ (ϵ 18,600). Infrared (chloroform): 2.99 μ .

N-Benzoyldiphenylamine-2-carboxylic Acid.¹⁵ A mixture of 24.5 g. (0.074 mole) of methyl N-benzoyldiphenylamine-2-carboxylate, 3.8 g. (0.070 mole) of sodium methoxide, 180 ml. of ethanol, and 75 ml. of water is heated under reflux for 2 hours. The resulting pale orange alkaline solution is diluted with water, washed once with ether, and acidified with excess hydrochloric acid. The precipitate is filtered and washed with water. After drying for 1 hour at 95°, 21 g. of crude product is obtained which, after recrystallization from acetone-pentane, affords white crystals, m.p. 190–193°. The yield is 18.9 g. (80% based on N-benzoyl ester).

Diphenylamine-2-carboxylic Acid.^{15,36} Two grams (0.006 mole) of methyl N-benzoyldiphenylamine-2-carboxylate is treated with a solution of 8 g. of potassium hydroxide in 20 ml. of water and 60 ml. of methanol. The mixture is heated under reflux for 2.5 hours, diluted with water, and a trace of insoluble material is removed by filtration. Excess hydrochloric acid is then added and the mixture is heated to boiling to dissolve benzoic acid. The insoluble product is filtered hot and washed with

boiling water to give a white powder, m.p. 169–179°. One recrystallization from ethanol-water gives 1.0 g. (77%) of product, m.p. 188.5–191°. Ultraviolet (ethanol): λ_{\max} 220 m μ (ϵ 21,800), 287 m μ (ϵ 13,900), 348 m μ (ϵ 6500). Infrared (KBr): 3.00 μ , 6.02 μ .

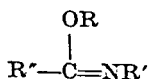
2,4,7-Tribromoacridone.¹⁰⁵ (a) N-Benzoyl-4,4',6-tribromodiphenylamine-2-carboxylic acid (5.0 g., 0.009 mole)^{15,105} is heated at 300–350° for a few minutes. The material is boiled with a little aqueous sodium hydroxide, then with water. Recrystallization from *m*-cresol furnishes 2.17 g. (56%) of pale yellow needles, m.p. >340°.

(b) A mixture of 1.0 g. (0.0018 mole) of methyl N-benzoyl-4,4',6-tribromodiphenylamine-2-carboxylate^{15,105} and 2.10 ml. of concentrated sulfuric acid is heated at 160–200° for about a minute. On cooling, the product crystallizes to give 0.66 g. (87%) of the acridone.

5-Methyl-1,2-benzacridone.⁴⁸ 2-Carbomethoxy-6-methylphenyl N- β -naphthylbenzimidate⁴⁸ (22 g., 0.056 mole) is heated at 360° under nitrogen for 0.5 hour. Methyl benzoate is formed and boils away. The residual solid is cooled, washed with benzene, and recrystallized from nitrobenzene to give 5.5 g. (38%) of yellow needles, m.p. 264–265°.

TABULAR SURVEY

In listing benzimidates



compounds with R = R' = phenyl are named first. Next, derivatives of phenol (R = phenyl, R' varies) are listed, and, last, compounds where R varies are listed. Within each group, monohalo derivatives are named first, followed by nitro-, hydroxy-, methoxy-, and alkyl-substituted compounds. Imidates with one carbonyl-containing substituent are named next. Finally, compounds with more than one substituent on the key radical are listed, followed by imidates derived from polycyclic and heterocyclic phenols.

In the tables a dash (—) indicates that a compound has been prepared but no yield was given. Omission of both the yield and the dash shows that the reaction leading to the compound in question was not attempted.

The literature coverage includes July, 1963.

All references to a particular listing are located in the last column. When multiple references occur, individual citations appear in parentheses under the appropriate heading.

¹⁰⁵ Acheson and Robinson, *J. Chem. Soc.*, 1953, 232.

TABLE I

ARYL N-ARYLBENZIMIDATES, N-AROYLDIARYLAMINES, AND DIARYLAMINES

Aryl N-Arylbenzimidate				Yield, % (Ref.)	Conditions for Rearrangement (Ref.)	N-Aroyldiarylamine $\text{R}''-\text{C}(=\text{O})-\text{N}(\text{R})-\text{R}'$ Yield, % (Ref.)	Diarylamine $\text{R}'\text{NHR}'$ Yield, % (Ref.)	References
R	Substituents in $\text{R}'-\text{C}(=\text{O})-\text{NR}'$	R'	R''					
C_6H_5	C_6H_5	C_6H_5	C_6H_5	64 (9)	240°; 1 hr. (1) 270-300°; 2 hr. (2)	—*	Complete transformation (2)	1-3, 9
C_6H_5	C_6H_5	C_6H_5	<i>o</i> -ClC ₆ H ₄	—	260°; 1.5 hr. (3)	71†		3
C_6H_5	C_6H_5	C_6H_5	<i>p</i> -ClC ₆ H ₄	—	270°; 1.5 hr.	63†		3
C_6H_5	C_6H_5	C_6H_5	<i>o</i> -O ₂ NC ₆ H ₄	—	270°; 1.5 hr.	62†		3
C_6H_5	C_6H_5	C_6H_5	<i>p</i> -O ₂ NC ₆ H ₄	—	270°; 1.5 hr.	49†		3
C_6H_5	C_6H_5	C_6H_5	<i>p</i> -ClH ₂ OC ₆ H ₄	—	267°; 1.5 hr.	85†		3
C_6H_5	C_6H_5	C_6H_5	2,4,6-Cl ₃ C ₆ H ₃	54	270°; 1.5 hr.	<55†		3
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	305-318°, 1 hr.	91		13
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	270°; 1.5 hr.	39†	85	3
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	270°; 1.5 hr.	49†		3
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	270°; 1.5 hr. (3)	61†	— (26)	3, 26
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	270°; 1.5 hr.	85†		3
C_6H_5	C_6H_5	C_6H_5	C_6H_5	63	280-300°; 2 hr.	—	Satisfactory	3
C_6H_5	C_6H_5	C_6H_5	C_6H_5	28	290-300°; 2 hr.	—	68	25
C_6H_5	C_6H_5	C_6H_5	C_6H_5	89	290°; 2 hr.	High	94§	24
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	270°; 1.5 hr.	36†		27
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	300-310°; 2 hr.	—		3
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	267°, 1.5 hr.	<17†		17
C_6H_5	C_6H_5	C_6H_5	C_6H_5	—	270°, 1.5 hr.	63†		3

*Note: References 106 and 107 are on p. 51.

Note: References 108 and 107 are on p. 51.

* The rearrangement was carried out as part of a kinetic study (ref. 9). The product was not isolated.

† This represents percent conversion (not percent yield) during a kinetic study at the temperature indicated (ref. 3). For preparative means, the rearrangement was carried out at 260-310°, but the yield was not given.

‡ The reaction was unsuccessful.

§ The yield is based on imidate.

TABLE I—Continued

ARYL N-ARYLBENZIMIDATES, N-ARYLDIARYLAMINES, AND DIARYLAMINES

Aryl N-Arylbenzimidate			Yield, % (Ref.)	Conditions for Rearrangement (Ref.)	N-Aroyldiarylamino $R''-\overset{\overset{R}{\parallel}}{C}-N(R')$ Yield, % (Ref.)	Diarylamino $R'NR''$ Yield, % (Ref.)	References
R	Substituents in $R''-\overset{\overset{OR}{\parallel}}{C}-NR'$	R'					
<i>p</i> -C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	55	305-310°; 1 hr.	85	85	13
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	92	280°; 18 hr.	80	96	12
<i>o</i> -C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	37 (9)	270-280°; 1 hr. (2)	91*†	—	2, 3, 9
<i>o</i> -C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	—	255°; 1.5 hr. (3)	—	—	18
<i>o</i> -C ₆ H ₄	<i>o</i> -C ₆ H ₄	C ₆ H ₅	—	—	—	—	10
<i>o</i> -C ₆ H ₄	<i>o</i> -C ₆ H ₄	C ₆ H ₅	—	200°; 2 hr.	—	—	3
<i>m</i> -C ₆ H ₄	<i>m</i> -C ₆ H ₄	C ₆ H ₅	—	255°; 1.5 hr.	84†	—	10
<i>m</i> -C ₆ H ₄	<i>m</i> -C ₆ H ₄	C ₆ H ₅	—	200°; 2 hr.	—	—	10
<i>m</i> -C ₆ H ₄	<i>m</i> -C ₆ H ₄	C ₆ H ₅	—	200°; 2 hr.	—	—	2, 3, 9
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	57 (9)	280-290°; 2 hr. (2)	92*†	—	15
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	90	255°; 1.5 hr. (3)	74	71	19
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	—	300°; 2 hr.	—	—	9, 16, 20
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	60 (9)	200°; 2 hr.	78 (20)*	94 (20)	15
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	—	—	—	—	15
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	90	200-320°; 2.5 hr.	76	—	15
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	48	250-270°; 2 hr.	76	85	21
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	51	155-200°; 2.5 hr.	86	87	0
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	75	255°	—	—	22
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	54 (9)	270-290°; 2 hr.	84	98	1, 3, 9
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	—	105°; 1 hr. (3)	40 (3)	—	30
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	67	170-180°; 1 hr.	—	—	104
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	30 (9)	—	—	—	3, 9
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	57	—	—	—	3, 9
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	29 (9)	200°; 1.5 hr.	74*†	—	3
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	—	200°; 1.5 hr.	55†	—	3, 9
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	60 (9)	200°; 1.5 hr.	41*†	—	0
<i>p</i> -C ₆ H ₄	<i>p</i> -C ₆ H ₄	C ₆ H ₅	10	255°	—	—	0

α -CH ₃ C ₆ H ₄ H ₄	p -CH ₃ C ₆ H ₄	C ₆ H ₅	—	—	—	19
α -CH ₃ C ₆ H ₄ H ₄	α -CH ₃ C ₆ H ₄	C ₆ H ₅	69	250–300°; 2 hr.	—	23
α -CH ₃ C ₆ H ₄ H ₄	m -CH ₃ C ₆ H ₄	C ₆ H ₅	—	250–300°; 2 hr.	Satisfactory	25
α -CH ₃ C ₆ H ₄ H ₄	p -CH ₃ C ₆ H ₄	C ₆ H ₅	Mod. good	250–300°; 2 hr.	6.2g	25
m -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	30 (24); 60 (6)	250–300°; 2 hr. (24)	85 (24)*	0, 24
m -CH ₃ C ₆ H ₄ H ₄	α -CH ₃ C ₆ H ₄	C ₆ H ₅	—	250–300°; 2 hr.	Isomerized completely	25
m -CH ₃ C ₆ H ₄ H ₄	p -CH ₃ C ₆ H ₄	C ₆ H ₅	—	275°	*	25
p -CH ₃ C ₆ H ₄ H ₄	α -CH ₃ C ₆ H ₄	C ₆ H ₅	64	280–300°; 2 hr.	—	9
p -CH ₃ C ₆ H ₄ H ₄	m -CH ₃ C ₆ H ₄	C ₆ H ₅	58	270–300°; 2 hr.	—	25
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	—	255°	—	2
α -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	15	255°	*	9
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	58	255°	*	9
α -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	30	255°	*	9
α -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	40	250°; 9 hr.	40	9
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	57	255°	*	0
p -CH ₃ C ₆ H ₄ H ₄	p -CH ₃ C ₆ H ₄	C ₆ H ₅	—	300°	Almost quantitative	27
α -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	67	275°; 2.5 hr.	86	28
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	74	275°; 2.5 hr.	83	29
α -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	35	270°; 40 min.	*	33
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	35	—	*	33
α -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	75 (26)	270–280°; 2 hr. (33)	81 (33)	33
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	57	300°; 2 hr. (26)	84 (26)	20, 33
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	—	277–290°	90	15
p -CH ₃ C ₆ H ₄ H ₄	C ₆ H ₅	C ₆ H ₅	—	—	61g	33

Note. References 106 and 107 are on p. 51.

* The rearrangement was carried out as part of a kinetic study (ref. 9). The product was not isolated.

† The percentages represent conversion (not percent yield) during a kinetic study at the temperature indicated (ref. 3). For preparative means, the rearrangement was carried out at 280–310°, but the yield was not given.

‡ The reaction was unsuccessful.

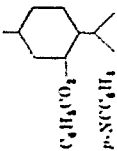
§ The yield is based on imide.

¶ The product is diphenylamine-4-carboxylic acid.

|| The product is N-benzoyl-4-chlorodiphenylamine-4-carboxylic acid.

TABLE I—Continued

ARYL, N-ARYLBENZIMIDATES, N-AROYLDIARYLAMINES, AND DIARYLAMINES

Aryl N-Arylbenzimidate		Substituents in R'-C(=O)-NR'		Yield, % (Ref.)	Conditions for Rearrangement (Ref.)	N-Aroyldiarylamine Yield, % (Ref.)	Diaryllamine R'NHR' Yield, % (Ref.)	References
R	R'	R'	R''					
	$C_6H_4CO_2H$	$p-ClC_6H_4$	C_6H_5	88	280–295°	—**	—	15
$p-NCC_6H_5$		$p-NCC_6H_4$	C_6H_5	82	280–300°; 1.25 hr.	—	70††	32
$p-NCC_6H_4$		$2-O_2N-4-NCC_6H_5$	C_6H_5	78	Boiling Dowtherm;	—	—	29
$p-NCC_6H_4$		$2-CH_3-4-NCC_6H_5$	C_6H_5	45	Boiling Dowtherm;	—	85	29
		C_6H_5	C_6H_5	—	1–2 hr.	—††	—	3
$o-CH_3CO_2C_6H_5$		C_6H_5	C_6H_5	—	267°; 1.5 hr.	92*†	—	3, 9
$p-CH_3CO_2C_6H_5$		C_6H_5	C_6H_5	45 (9)	242°; 1.5 hr. (3)	29	—§§	35
$o-CH_3O_2CCH_2C_6H_4$		C_6H_5	C_6H_5	74	268°; 45 min.	90	89	31
$p-C_6H_4CO_2C_6H_4$		C_6H_5	C_6H_5	82	270–280°; 40 min.	93†	—	3
$2,4-Cl_2C_6H_3$		C_6H_5	C_6H_5	—	242°; 1.5 hr.	—	—	15
$2,4-Cl_2C_6H_3$		$p-ClC_6H_4$	$p-CH_3C_6H_4$	—	280–300°; 2.5 hr.	—	—	19
$2,4-Cl_2C_6H_3$		$o-CH_3C_6H_4$	C_6H_5	—	—	—	—	4
$2,4-Cl_2C_6H_3$		$2,4-Cl_2C_6H_3$	C_6H_5	—	280–300°; 2 hr.	—	—	17
$3,5-Cl_2C_6H_3$		$2,4-Cl_2C_6H_3$	C_6H_5	—	—	—	—	106
$4-Cl-2-BrC_6H_3$		$3,5-Cl_2C_6H_3$	C_6H_5	71	230–240°; 2.5 hr.	42–55	71–79	29
$2-Cl-4-NCC_6H_5$		$o-BrC_6H_4$	C_6H_5	25	Boiling Dowtherm;	84	60	29
		$p-NCC_6H_4$	C_6H_5	—	1–2 hr.	—	—	29
		$2-CH_3-4-NCC_6H_5$	C_6H_5	36	Boiling Dowtherm;	80	73	29
		$2-BrC_6H_4$	C_6H_5	—	1–2 hr.	—	—	106
$(2-Br-4-C_6H_4)N_2H_5$		$p-NCC_6H_4$	C_6H_5	74	240–255°; 2.5 hr.	68–80	78	29
$2-O_2N-4-NCC_6H_5$		$p-NCC_6H_4$	C_6H_5	60	Boiling anisole or pyridine	99	—	29
$2-O_2N-4-NCC_6H_5$		$2-O_2N-4-NCC_6H_5$	C_6H_5	96	Boiling Dowtherm;	—	86	29
$2-CH_3O-4-NCC_6H_5$		$p-NCC_6H_4$	C_6H_5	60	1–2 hr.	88	—	29

2-CH ₃ -4-NCC ₆ H ₃	p-NCC ₆ H ₄	C ₆ H ₅	70	Boiling Dowtherm; 1-2 hr.	94	85	29
2-CH ₃ -4-NCC ₆ H ₃	2-CH ₃ -4-NCC ₆ H ₃	C ₆ H ₅	83	Boiling Dowtherm; 1-2 hr.	94	33	29
2,4,6-Cl ₃ C ₆ H ₃	C ₆ H ₅	C ₆ H ₅	—	220°; 1.5 hr. (3)	>91†	— (4)	3, 4
2,4,6-Cl ₃ C ₆ H ₃	o-ClC ₆ H ₄	C ₆ H ₅	—	250-270°; 2 hr.	—	80	4
2,4,6-Cl ₃ C ₆ H ₃	p-ClC ₆ H ₄	C ₆ H ₅	80	250-270°; 2 hr.	—	80	4
2,4,6-Cl ₃ C ₆ H ₃	2,4-Cl ₂ C ₆ H ₃	C ₆ H ₅	88	250-270°; 2 hr.	81	92	15
2,4,6-Cl ₃ C ₆ H ₃	2,4,6-Cl ₃ C ₆ H ₃	C ₆ H ₅	—	280-300°	—	—	3
2,4,6-Cl ₃ C ₆ H ₃	p-CH ₃ OC ₆ H ₄	C ₆ H ₅	65	—	—	—	23
2,4,6-(NO ₂) ₃ C ₆ H ₃	C ₆ H ₅	C ₆ H ₅	—	—	—	—	1
2,4,6-(NO ₂) ₃ C ₆ H ₃	o-CH ₃ C ₆ H ₄	C ₆ H ₅	—	—	—	—	1
2,6-Cl ₄ -4-NCC ₆ H ₃	p-NCC ₆ H ₄	C ₆ H ₅	24	Boiling Dowtherm; 1-2 hr.	54	—	29
2,6-Cl ₄ -4-CH ₃ C ₆ H ₃	p-CH ₃ OC ₆ H ₄	C ₆ H ₅	75	Boiling C ₆ H ₅ OC ₆ H ₄ - 10 min.	56	—	23
4,6-1,2-2-CH ₃ C ₆ H ₃	p-CH ₃ OC ₆ H ₄	C ₆ H ₅	90	—	—	—	23
2,6-1,2-4-CH ₃ C ₆ H ₃	p-CH ₃ OC ₆ H ₄	C ₆ H ₅	—	—	—	—	23
2,6-1,2-4-CH ₃ O ₂ CC ₆ H ₃	p-CH ₃ OC ₆ H ₄	C ₆ H ₅	71	Boiling o-C ₆ H ₄ Cl ₂ , 80 min	95	—	23
2,6-1,2-4-n-C ₄ H ₉ O ₂ CC ₆ H ₃	p-CH ₃ OC ₆ H ₄	C ₆ H ₅	92	—	—	—	23
2-Br-6-CH ₃ O-4-CH ₃ O ₂ CC ₆ H ₃	2,6-(CH ₃) ₂ C ₆ H ₃	C ₆ H ₅	61	266°, 1.5 hr.	80†	—	34
2-C ₁₀ H ₇	C ₆ H ₅	C ₆ H ₅	—	266°, 1.5 hr.	82†	—	3
β-C ₁₀ H ₇	C ₆ H ₅	C ₆ H ₅	—	280°, 20 min.	72	—	3
8-Quinoliny	o-ClC ₆ H ₄	C ₆ H ₅	74	—	—	—	30
8-Quinoliny	o-CH ₃ C ₆ H ₄	C ₆ H ₅	71	280°, 10 min.	—	—	30
8-Quinoliny	2-Br-4-CH ₃ C ₆ H ₃	C ₆ H ₅	47	—	—	—	30
8-Quinoliny	2-Br-4,6-(CH ₃) ₂ C ₆ H ₃	C ₆ H ₅	62	—	—	—	30
5,7-Cl ₂ -8-quinoliny	C ₆ H ₅	C ₆ H ₅	66	—	—	—	30
		C ₆ H ₅	21	260°, few min.	—	—	30

Note. References 106 and 107 are on p. 51.

* The rearrangement was carried out as part of a kinetic study (ref. 9). The product was not isolated.

† The product was not isolated.

‡ The reaction was unsuccessful.

§ The initial product decomposes at once to 1-menthene, benzoic acid, and 2-chloroaniline.

|| The product was obtained by pyrolysis of 4,4-diamidino-N-benzoyldiphenylamine.

¶ 1,2-Diphenyl-1,4-quinone was obtained

§§ N-Phenylmaleimide was obtained

For preparative means, the rearrangement was

TABLE II

DIARYLAMINE-2-CARBOXYLIC ACIDS

Aryl N-Arybenzimidate Substituents in		N-Aryldiarylamines		Diarylamines- 2-carboxylic Acid		Acridone
R	R'	Yield, % (Ref.)	Yield, % (Ref.)	Yield, % (Ref.) ^a	Substituent	
Conditions for Rearrangement		2-Carboxylic Ester	2-Carboxylic Acid	2-Carboxylic Acid		
H	C ₆ H ₅	62 (36), 81 (15)	73 (15)	78 (36) 96 (15)	—	15, 36
H	<i>o</i> -ClC ₆ H ₄	—	—	—	—	107
H	<i>p</i> -ClC ₆ H ₄	88	85-91	76	2-Cl	15
H	<i>o</i> -CH ₃ O ₂ CC ₆ H ₄	70	83	—	—	87
H	<i>o</i> -C ₆ H ₄ O ₂ CC ₆ H ₄	63	91	—	—	44
H	2,4-Cl ₂ C ₆ H ₃	72	65	—	—	15
H	2,4-(CH ₃) ₂ C ₆ H ₃	56	89	74	2,4-(CH ₃) ₂	15
3 Cl	<i>p</i> -CH ₃ OC ₆ H ₄	—	—	—	1-Cl-7-OCH ₃	71
						46

Note: References 100 and 107 are on p. 51.

^a The yield is based on the N-benzoyl ester.

^b The reaction was unsuccessful.

^c 2-Carboxyphenylamine-2-acetic acid was obtained.

^d The yield is based on methyl 6-chlorosalicylate.


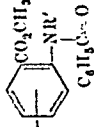
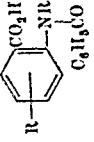
^e The 6-chloroacridone was synthesized



^a Pyrolysis of N-benzoyl ester.

^b Pyrolysis of N-benzoyl ester acid.

^c Treatment of diarylamines, RNHR', with POCl₃ followed by hydrolysis.

TABLE II—Continued
DIARYLAMINE-2-CARBOXYLIC ACIDS

Aryl N-Arylbenzimidate		N-Aroyldiarylamino		Diarylamine-2-carboxylic Acid		Yield, % (Ref.) ^a	Yield, % (Ref.) ^a	Substituent	Method (Ref.)	Yield, %	Refs.
R	R'	Substituents in 	Conditions for Rearrange- ment	2-Carboxylic Ester 	2-Carboxylic Acid 						
4-Cl	p-CH ₃ OC ₆ H ₄	—	200–210°; 10 min.	—	—	—	—	2-Cl-7-OCH ₃	b	Almost quant.	15
5-OCH ₃	o-ClC ₆ H ₄	86	270°; 10 min.	—	—	—	—	5-Cl-3-OCH ₃	a, b	—	40
5-OCH ₃	m-ClC ₆ H ₄	83	—	—	—	—	—	1-Cl-8-OCH ₃ ^{a, b}	c	—	41
5-OCH ₃	p-ClC ₆ H ₄	83	270–310°	80	—	—	77	2-Cl-6-OCH ₃	a, b, c	—	42
5-OCH ₃	p-FC ₆ H ₄	50	275–300°	—	—	—	—	2-1-6-OCH ₃	a, c	—	43
6-CH ₃	C ₆ H ₅	—	200°	92	—	—	—	—	—	—	37
6-CH ₃	o-FC ₆ H ₄	61	275°	81	—	—	—	—	—	—	34
6-CH ₃	o-ClC ₆ H ₄	72 (36)	200–270° (37)	88 (37)	92 (36)	—	—	4-Cl-5-CH ₃	b (36)	80	36, 37
6-CH ₃	75 (37)	—	—	—	—	—	—	—	—	—	34
6-CH ₃	o-BrC ₆ H ₄	—	280°	80	—	—	—	—	—	—	37
6-CH ₃	o-CH ₃ C ₆ H ₄	60	200°	—	—	—	—	—	—	—	38
6-CH ₃	p-CH ₃ C ₆ H ₄	—	276°	70	98	—	—	—	—	—	34
6-CH ₃	2,4-Cl ₂ C ₆ H ₃	69	285–290°	70	—	—	—	—	—	—	34
6-CH ₃	2-Cl-4-BrC ₆ H ₃	—	275°	83	—	—	—	—	—	—	34
6-CH ₃	2-Cl-4-CH ₃ OC ₆ H ₃	—	285°	82	—	—	—	—	—	—	34
6-CH ₃	2-Cl-4-CH ₃ C ₆ H ₃	—	285–290°	79	—	—	—	—	—	—	34
6-CH ₃	2,4,6-(CH ₃) ₃ C ₆ H ₃	—	—	†	—	—	—	5-CH ₃ -3,4- benzo	a	72	48
6-CH ₃	2,4,6-(CH ₃) ₃ C ₆ H ₃	70	270–300°; 15 min.	††	—	—	—	5-CH ₃ -1,2- benzo	a	38	48
6-CH ₃	2,4,6-(CH ₃) ₃ C ₆ H ₃	63	300°; 0.5 hr.	††	—	—	—	—	—	—	48

4,6-Cl ₂ C ₆ H ₄	84	220°	89	—	2,4,5,7-Cl ₄	d	10	37
4,6-Cl ₂ 2,4-Cl ₂ C ₆ H ₃ ††	85	260°; 10 ml.	—	—				47
4,6-Br ₂ C ₆ H ₄	86	100–200°	80	—				34
4,6-Br ₂ p-BrC ₆ H ₄	85 (15)	270° (15)	87 (15)	—	2,4,7-Br ₃	b	50 (105)	81
	200–210° (105)		86–84 (105)	—		c	91 (15)	15, 105
4,6-Br ₂ 2,4-Br ₂ C ₆ H ₃	—	260°; 5 ml.	80	*	2,4,5,7-Br ₄	d	87 (105)	105
						d	66	
	—	240–320°; 15 ml.	††		1,2,7,8-Dibenzo	a	80	49
	74	280–300°; 0.5 hr	††		3,4,5,6-Dibenzo	a	47	49
	51	350–360°	††		1,2,6,7-Dibenzo	a	54	48

Note. References 106 and 107 below.

* The yield is based on the N-benzoyl ester.

† The reaction was unsuccessful.

‡ Both the methyl and the ethyl esters were used.

§ This is the probable structure of the product.

†† Pyrolysis gave the acetone directly.

‡‡ The ethyl ester was used instead of the methyl ester.

a Pyrolysis of N-benzoyl ester

b Pyrolysis of N-benzoyl acid.

c Treatment of diarylamine, RNHR', with POCl₃ followed by hydrolysis.

d Treatment of the ester with sulfuric acid.

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CHAPTER 2

α -AMIDOALKYLATIONS AT CARBON

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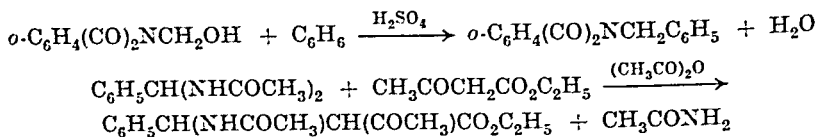
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INTRODUCTION

This chapter is concerned with reactions which lead to the formation of a new carbon-carbon bond by replacement of X from the electrophilic reagent $\text{RCON}(\text{R}')\text{CH}(\text{R}'')\text{X}$, where X is halogen, $-\text{OH}$, $-\text{OR}$, $-\text{OCOR}$, $-\text{NHCOR}$, $-\text{NR}_2$ or $-\text{NR}_3^{\oplus}$. The group R' may be hydrogen or alkyl or, in important instances, a second acyl group, as in the corresponding derivatives of phthalimide, $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}(\text{R}'')\text{X}$. In a few cases a sulfonyl group may replace the acyl group of the electrophilic reagent.

The nucleophiles that react with these reagents fall into two broad groups: aromatic compounds and aliphatic compounds containing reactive methylene or methine groups. The first may be illustrated by the phthalimidomethylation of benzene, and the second by the reaction of ethyl acetoacetate with $\text{N,N}'$ -benzylidenebisacetamide.



Also included in this review are the methods for preparing the electrophilic reagents. They are followed by a listing of compounds structurally related to them, and which, consequently, must be regarded as potential amidoalkylating agents. Portions of the material in this chapter have been reviewed elsewhere.^{1,2}

MECHANISMS OF THE REACTIONS

The reactions considered in this chapter include acid-catalyzed, base-catalyzed, and thermally induced processes. They, like the corresponding α -aminoalkylation reactions,³ probably encompass a considerable portion of the mechanistic spectrum of heterolytic organic chemistry. Detailed studies are almost completely lacking. Nevertheless, some general outlines of the mechanistic possibilities can be drawn.

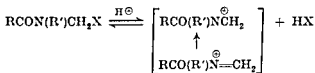
Although cryoscopic studies in 100% sulfuric acid have yet to be reported, it seems likely that, in very strong acids of high dielectric constant, electrophiles lacking a hydrogen atom on the nitrogen atom undergo appreciable dissociation to a carbonium-immonium ion. In the

¹ Hellmann, *Angew. Chem.*, **69**, 463 (1957).

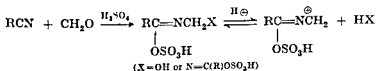
² Schröter in *Houben-Weyl Methoden der Organischen Chemie*, Vol. XI/1, 4th ed., G. Thieme, Stuttgart, 1957, pp. 795-895.

³ Hellmann and Opitz, *α -Aminoalkylierung*, Verlag Chemie, GMBH, Weinheim, 1960, pp. 64-79.

presence of weak nucleophiles (e.g., aromatic rings) bimolecular electro-



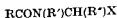
philic displacement (S_E2) of protons from C—H bonds usually follows. Under the same conditions amide derivatives having a hydrogen atom attached to the nitrogen atom ($\text{R}' = \text{H}$) may give the analogous cation, but other forms are more likely. Thus, when nitriles are treated with formaldehyde in strong sulfuric acid, sulfur-containing intermediates have been isolated.^{4,5} Evidence indicates that these are sulfate esters which in strong acid equilibrate with their corresponding carbonium ions.⁴⁻⁶ Granting the existence of these structures, identical species should, of course, be formed when the amide, $\text{RCONHCH}_2\text{X}$, is dissolved in strong



sulfuric acid. That such a common electrophilic intermediate is present is suggested by the recent finding that nitriles and formaldehyde in either strong sulfuric or strong phosphoric acid can substitute effectively for the corresponding methylolamides in the amidomethylation of aromatic compounds.⁵

In acid-catalyzed processes associated with media of low dielectric constant it is unlikely that appreciable preformed concentrations of carbonium ions are present. In such processes, reaction with weak nucleophiles probably involves either tight ion pairs or incipient carbonium ions formed by an S_N1 process.

Reactions in neutral or basic media of amide derivatives



lacking a hydrogen atom on the nitrogen atom exhibit characteristics of S_N2 processes. Thus, more nucleophilic reactants are usually required under these conditions, and reactivity toward comparable nucleophiles generally diminishes with decreasing stability of the leaving group X,

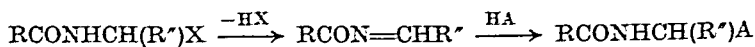
i.e., halide ion $\sim \text{R}_3\text{N}^\oplus > \text{OH}^\oplus \sim \text{OR}^\oplus$. It must be recognized, however,

⁴ Magat, Faria, Reith, and Salisbury, *J. Am. Chem. Soc.*, **73**, 1028 (1951).

⁵ Parris and Christenson, *J. Org. Chem.*, **25**, 1888 (1960).

⁶ Mowry and Ringwald, *J. Am. Chem. Soc.*, **72**, 4439 (1950).

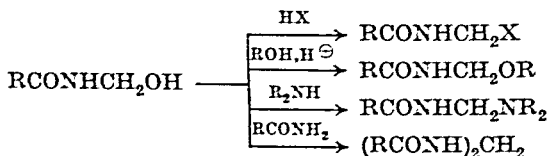
that even under these conditions the presence of proton donors can assist the removal of X by an acid-catalyzed process. These considerations also apply to similar reactions of amide derivatives with $R' = H$, but with the added opportunity for a mechanism involving an azomethine intermediate. This elimination-addition scheme appears to provide the most attractive mechanism for most of the thermally induced amidoalkylation reactions.



SCOPE AND LIMITATIONS

General Considerations

The N-methylol-amides and -imides are the most important electrophiles to be dealt with here. They are readily prepared by the reaction of formaldehyde with primary amides and imides, and their stability toward heat and acid is sufficient to permit their use under drastic reaction conditions. Furthermore, they can be employed as intermediates for the preparation of most of the other useful electrophiles.



Unlike formaldehyde, most higher aldehydes in their reactions with amides do not stop at the $RCHOHNHCOR'$ stage but react further to produce N,N'-alkylidenebisamides, $RCH(NHCOR')_2$. Thus, whereas the amidomethylation reaction permits a relatively broad selection of electrophilic reagents, the homologous α -amidoalkylation reactions have been restricted almost exclusively to the use of N,N'-alkylidene- and N,N'-arylidene-bisamides. As the reactivities of these derivatives often are to be found at the lower end of the electrophilic scale, their usefulness is further limited by the consequent requirement of comparatively high nucleophilic reactivity for the other reactant.

Structural Considerations

Structure of the Electrophile. Any structural feature tending to stabilize an incipient carbonium ion in either an S_N1 or an S_N2 process must enhance the rate of reaction with a given nucleophile. However, if ionization is not rate-limiting, the reverse is true, since stabilization of

a *preformed* cation must thereby decrease its tendency to lose its charge through electrophilic attack. Therefore, in going from reaction conditions where an S_N1 or S_N2 mechanism prevails to a situation favoring the rapid pre-equilibrium production of carbonium ions (solvated or paired), one would expect to encounter an inversion in the reactivity sequence of a series of electrophiles. No quantitative work has been reported for α -amidoalkylation reagents. Nevertheless, indication that such an inversion in sequence applies to these reagents follows from a qualitative consideration of the results of several workers.

de Diesbach studied the reactions of a series of N-methylolamides in concentrated sulfuric acid at room temperature.⁷ He found that amido-methylation of 1,3-dimethylantraquinone in the 4-position succeeded with N-methyloltrichloroacetamide and N-methylolphthalimide but failed with N-methylolbenzamide. Phenanthrenequinone gave both a 2-mono- and a 2,7-di-substituted product with N-methyloltrichloroacetamide and N-methylolphthalimide, but only the monosubstitution product with N-methylolchloroacetamide. 2,4-Dimethylbenzophenone gave both a 5-mono- and a 3,5-di-substituted product with N-methylolphthalimide, but only the monosubstitution product with N-methyloltrichloroacetamide. These results enable one to construct the qualitative reactivity sequence: $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OH} > \text{CCl}_3\text{CONHCH}_2\text{OH} > \text{CH}_2\text{ClCONHCH}_2\text{OH} > \text{C}_6\text{H}_5\text{CONHCH}_2\text{OH}$. This order is the reverse of that expected for the stabilities of the corresponding carbonium ions (i.e., delocalization of the

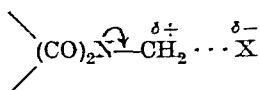
type $\text{RCONHCH}_2^{\oplus} \leftrightarrow \text{RCONH}=\text{CH}_2^{\oplus}$ should be greatest for the benzamide derivative) and suggests that, in *concentrated sulfuric acid*, reactivity is determined by the relative electrophilicities of preformed carbonium ions.

Tawney and co-workers prepared N-methylol- and N-chloromethylmaleimide and compared their chemical properties with those of the corresponding phthalimide derivatives.⁸ Although direct comparisons of their reactivities with aromatic compounds were not made, these investigators did establish that the hydroxyl group of N-methylolmaleimide was readily displaced by amines in dioxane solution and by *o*-nitrotoluene in concentrated sulfuric acid, and that N-chloromethylmaleimide readily underwent the zinc chloride-catalyzed reaction with benzene and phenol. However, unlike the corresponding phthalimide derivatives, N-methylolmaleimide would not react with hydrochloric acid to give the N-chloromethyl derivative, nor would the latter solvolyze in ethanol to give N-ethoxymethylmaleimide. Tawney and co-workers explained these striking differences by suggesting that the nitrogen atom in the maleimide,

⁷ de Diesbach, *Helv. Chim. Acta*, **23**, 1232 (1940).

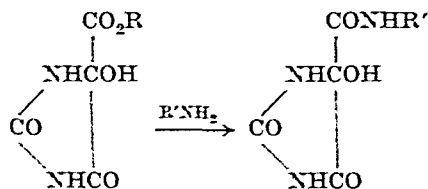
⁸ Tawney, Snyder, Conger, Leibbrand, Stiteler, and Williams, *J. Org. Chem.*, **26**, 15 (1961).

being more electronegative than that in the phthalimide, renders stabilization of the *incipient* carbonium ion



less effective in the former derivative. In an S_N1 process this would retard rate-limiting ionization, and in an S_N2 process it would make bond forming more important in the transition state and require a greater nucleophilicity of the attacking reagent.

The ultimate effect of this trend can be approached by substituting other electronegative groups directly on the methylol carbon atom. Esters of 5-hydroxy-5-hydantoincarboxylic acid gave only the corresponding amides with primary amines.⁹ The hydroxyl group remained unaffected. Apparently, so many electronegative groups are attached



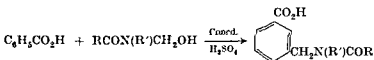
to the usually reactive methylol carbon atom that insufficient development of positive charge in the transition state is available even for the attack of strongly nucleophilic amines. One might predict, however, that, if a carbonium ion could be generated from this or related hydroxyhydantoins, electrophilic reagents more reactive than anything obtainable from the simple methylolamides would be produced.

Clearly, in an electrophilic reagent that reacts by a pre-equilibrium dissociation the nature of the anionic leaving group is immaterial. The most easily accessible derivative then becomes the reagent of choice. In view of the ready availability of N-methylolamides, it is not surprising that they have been used to the virtual exclusion of other α -amidoalkyl derivatives *when strong sulfuric acid is the reaction medium*. It is only under less drastic reaction conditions, or when a more active nucleophile is involved, that the stability of the group departing from the electrophile becomes significant. This will become more apparent from a consideration of the effect of nucleophile structure on the scope of these reactions.

Structure of the Nucleophile. As already indicated, two general groups of nucleophiles fall within the scope of this chapter: aromatic

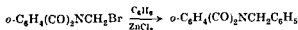
compounds and aliphatic compounds containing an active hydrogen atom attached to a carbon atom. The range of aromatic reactivity can best be illustrated by consideration of four examples: benzoic acid, benzene, phenol, and 2-naphthol.

As expected of such a poor nucleophile, benzoic acid requires reaction conditions ensuring attack by a strongly electrophilic species. Thus all the successful amidomethylations of benzoic acid so far reported involve reaction of a methylolamide in concentrated sulfuric acid at room temperature. Although N-methylolbenzamide gives the 3-amidomethylated product in only 8% yield under these conditions,¹⁰ N-methylolchloroacetamide¹¹ and N-methylolphthalimide¹² are converted in 54% and 60% yields, respectively. Again, these results agree with expectations based



on previous considerations of relative electrophilic reactivities in strong sulfuric acid.

Benzene is readily substituted under similar conditions. Indeed, a 32% yield of a 1,4-disubstituted product has been reported with N-methylolbenzamide in concentrated sulfuric acid.¹³ Such drastic conditions, however, are not required for simple substitution. Although N-bromomethylphthalimide is inert in boiling benzene, addition of a trace of anhydrous zinc chloride suffices to catalyze an exothermic reaction leading to N-benzylphthalimide in 94% yield.¹⁴



Phenol, which does not react with N-methylolphthalimide in boiling benzene, is readily attacked by N-bromomethylphthalimide under similar conditions even in the absence of a Lewis acid catalyst. A 51% yield of a mixture of approximately equal amounts of 2- and 4-phthalimidomethylphenol is obtained.¹⁵ Interestingly, no 2,4-diphthalimidomethylphenol

¹⁰ Linhorn, Bischoff, and Szelinski, *Ann.*, **343**, 223 (1905).

¹¹ Einhorn and Mauermayer, *Ann.*, **343**, 282 (1905).

¹² Oda, Teramura, Tanimoto, Nomura, Suda, and Matsuda, *Bull. Inst. Chem. Res. Kyoto Univ.*, **33**, 117 (1955) [*C.A.*, **51**, 11355 (1957)].

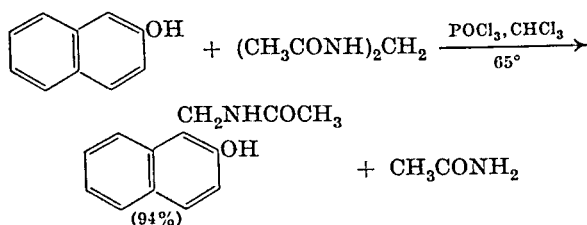
¹³ Neutzeescu and Dinulescu, *Rev. Chim. Acad. Rep. Populaire Roumaine*, **2**, 47 (1954), *Commun. Acad. Rep. Populaire Române*, **4**, 45 (1954) [*C.A.*, **50**, 15445 (1956)].

¹⁴ H. J. Zaugg, unpublished data.

¹⁵ Zaugg and Schaefer, *J. Org. Chem.*, **28**, 2925 (1963).

is formed. This material accounts for 32% of the product when phenol is treated with N-methylolphthalimide in concentrated sulfuric acid.^{15,16}

2-Naphthol represents a near approach to the ultimate in nucleophilic reactivity toward α -amidoalkylation reagents. At room temperature in an ethanol solution containing 1–2% of hydrochloric acid, it reacts with N-methylolbenzamide to give 1-benzamidomethyl-2-naphthol quantitatively in 2 hours.¹⁰ (The more nucleophilic aromatic heterocycles, such as the polymethylpyrroles,¹⁷ also resemble 2-naphthol in their reactivity toward various methylolamides.) 2-Naphthol is sufficiently nucleophilic to undergo smooth α -amidoalkylation with N,N'-methylene- and N,N'-arylidene-bisamides.¹⁸ Although phenols and even phenol ethers and



esters react in like manner, the diminished reactivity of the bisamides clearly restricts their usefulness in the aromatic series to substitution in activated rings.

Conceivably, aromatic nucleophilicity could be increased by employing an aromatic Grignard reagent. The orientational ambiguity often associated with the direct substitution methods also would be obviated thereby. The only example of this approach however, appears to be the reaction of phenylmagnesium bromide with N-benzoyldiphenylketimine (see p. 77).¹⁹

Aliphatic compounds containing methyl, methylene, or methine groups sufficiently reactive to undergo α -amidoalkylation represent a wide variety of structural types. They include cyclic and acyclic β -dicarbonyl compounds of all types, β -cyano esters, activated nitriles, nitro alkanes and β -nitro esters, certain non-aromatic heterocyclic compounds with active methine groups in the ring, heteroaromatic compounds with activated methyl groups, acetylene, and hydrocyanic acid. Most of these types possess nucleophilic reactivity in the range of that possessed by phenol in the aromatic series. Hence some of them can undergo reaction with the whole range of α -amidoalkylation reagents, including the weakly

¹⁶ Tscherniac, Ger. pat. 134, 979 (*Chem. Zentr.*, 1902, 11, 1084).

¹⁷ Fischer and Nenitzescu, *Ann.*, **443**, 113 (1925).

¹⁸ Ishidate, Sekiya, and Yamahara, *Chem. Ber.*, **93**, 2898 (1960).

¹⁹ Ivanoff, *Doklady Akad. Nauk SSSR*, **109**, 537 (1956) [*C.A.*, **51**, 4997 (1957)].

electrophilic N,N'-bisamides. However, unlike the aromatic nucleophiles, many of the reactive methylene compounds are unstable or undergo side reactions in strong acid. For this reason and because their corresponding anions invariably exhibit enhanced nucleophilic reactivities, α -amidoalkylations of these weak aliphatic acids are usually conducted in neutral or basic media.

α -Amidoalkylation of Aromatic Carbon Atoms

With N-Methylol-amides and -imides (the Tscherniac-Einhorn Reaction). In 1902 Tscherniac reported the condensation of N-methylol-phthalimide with a series of aromatic compounds in concentrated or fuming sulfuric acid.¹⁶ Subsequently Einhorn extended the reaction to a variety of readily available N-methylolamides.^{10,11,20-26} The Tscherniac-Einhorn reaction,^{1,2} together with its more recently developed variations (see below), bears a superficial relationship to the well-known Mannich



reaction.^{3,27} However, the latter is usually restricted to the preparation of tertiary benzylamines, whereas amidomethylation, through hydrolysis of initial products, provides a route to primary benzylamines. Furthermore, the scope of the Mannich reaction in the aromatic series is generally restricted to phenols or to equally nucleophilic ring systems. In contrast, some of the reagents available for amidomethylation are even more electrophilic than the usual acylation reagents of the Friedel-Crafts reaction. Consequently the scope of some of the amidomethylations can be extended to aromatic systems usually considered rather inert to substitution.

The facile amidomethylation of benzoic acid has already been discussed. Although experimental details have been reported only for chlorobenzene,¹³ successful amidomethylation of the other halobenzenes and of benzonitrile and benzenesulfonamide has been claimed.²⁸ Benzophenone reportedly is inert to N-methylolamides in concentrated sulfuric acid, but

¹⁰ Einhorn, Ger. pat. 156,398 (*Chem. Zentr.*, 1905, I, 55)

¹¹ Einhorn and Göttler, *Ber.*, 42, 4837 (1909)

²⁰ Einhorn and Ladisch, *Ann.*, 343, 264 (1905)

²¹ Einhorn and Ladisch, *Ann.*, 343, 265 (1905)

²² Einhorn and Ladisch, *Ann.*, 343, 277 (1905)

²³ Einhorn and Schupp, *Ann.*, 343, 252 (1905)

²⁴ Einhorn and Sprongerts, *Ann.*, 361, 161 (1908)

²⁷ Blucke, in Adams, *Organic Reactions*, Vol. I, John Wiley & Sons, New York, 1942, p. 303.

²⁸ O'Cinnéide, *Nature*, 175, 47 (1955).

its methyl and hydroxyl derivatives are easily substituted.⁷ Even nitrobenzene is subject to attack. In his original patent Tscherniac stated that a 3-substituted nitrobenzene could be obtained from N-methylolphthalimide either in concentrated sulfuric acid at 50° or in fuming sulfuric acid at room temperature.¹⁶ More recently the isolation of 3,5-bisphthalimidomethylnitrobenzene has been reported using 20% oleum as the condensing agent.²⁹

Because of its clear superiority over other readily available reagents, N-methylolphthalimide has been used most frequently in the Tscherniac-Einhorn reaction. This superiority arises from the high order of stability and reactivity of N-methylolphthalimide in strong sulfuric acid and from its ability to form crystalline readily isolable products from which, if desired, the phthalimido group can be removed easily.³⁰ Notwithstanding the fact that benzamides are generally more difficult to hydrolyze than trichloroacetamides or even chloroacetamides, N-methylolbenzamide is used as frequently as the methylol derivatives of the two preceding halogenated amides. Examples of the use of N-methylol derivatives of most of the commonly available amides or imides are to be found. Yet, aside from their requirement for the synthesis of specifically desired derivatives, none appears to provide any particular advantage over the generally preferred reagents. The hitherto unreported N-methyloltrifluoroacetamide, $\text{CF}_3\text{CONHCH}_2\text{OH}$ (see p. 130), however, might show some superiority over the common reagents. In strong sulfuric acid it should be even more reactive than its trichloro analog, and the extraordinary ease of alkaline hydrolysis of trifluoroacetamide derivatives³¹ would make it a convenient reagent for the preparation of benzylamines.

Because they are more difficult to isolate, N-methylol derivatives of monosubstituted amides, i.e., $\text{RCON(R')CH}_2\text{OH}$, are seldom used.^{32,33} However, Buc has avoided this difficulty in the case of the two lactams, 2-pyrrolidinone and γ -valerolactam, merely by using a mixture of the amide and paraformaldehyde in concentrated sulfuric acid.³⁴

N,N'-Dimethylol derivatives of dicarboxamides and of urea have also been employed. For example, 1,3-dimethylolurea (1) and ethyl 2-furoate condense in concentrated sulfuric acid to give the symmetrically disubstituted urea 2 in 93% yield.³⁵ N,N'-Dimethyloloxamide,

²⁹ Buc, U.S. pat. 2,593,840 [C.A., 46, 6844 (1952)].

³⁰ Ing and Manske, *J. Chem. Soc.*, 1926, 2348; Sheehan and Frank, *J. Am. Chem. Soc.*, 71, 1656 (1949).

³¹ Weygand and Reiher, *Chem. Ber.*, 88, 26 (1955), and previous references.

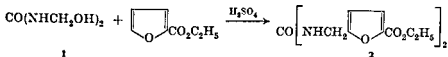
³² Böhme, Dick, and Driesen, *Chem. Ber.*, 94, 1679 (1961).

³³ Böhme, Driesen, and Schünemann, *Arch. Pharm.*, 294, 344 (1961).

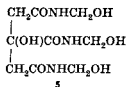
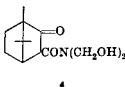
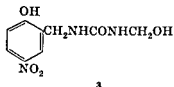
³⁴ Buc, U.S. pat. 2,652,403 [C.A., 48, 11495 (1954)].

³⁵ Moldenhauer, Irion, and Marwitz, *Ann.*, 583, 37 (1953).

(CONHCH₂OH)₂, reacts similarly.³⁵ Several reactions of 1,3-dimethylol-



urea have been reported in which only one of the reactive centers is attacked.³⁶⁻⁴⁰ Thus, with 4-nitrophenol in sulfuric acid diluted with glacial acetic acid, the unsymmetrical urea **3** is obtained.⁴⁰ Although a



few N,N-dimethylolamides of type **4** are known,^{41,42} as is N,N',N''-trimethylolcitramide (**5**),⁴³ Tscherniac-Einhorn reactions with such polyfunctional derivatives have not been reported.

A large majority of aromatic amidomethylations reported to date have been conducted either in concentrated sulfuric acid according to Tscherniac's original specifications or in the ethanolic hydrogen chloride medium used by Einhorn for substitution of the more nucleophilic aromatic systems. Despite its long history, remarkably few attempts to vary the conditions of the Tscherniac-Einhorn reaction have been reported. Even fewer qualify as reasonably systematic studies of reaction conditions. A careful investigation of the phthalimidomethylation of acetanilide has been reported by Ota, Kaneyuki, and Matsui.⁴⁴ They studied the effect of varying the sulfuric acid concentration on the reaction of equivalent quantities of acetanilide (16 g.) and N-methylolphthalimide (2.0 g.) at room temperature for 24 hours. In 99.5% sulfuric acid (8 ml.) only the *ortho* **6** and *para* **7** monosubstitution products were formed in 27 and 60% yields, respectively. However, in 4% oleum the yield of **7** decreased to

³⁵ de Diesbach, Swiss pat. 127,926-127,930 (*Chem. Zentr.*, 1929, I, 2243).

³⁷ de Diesbach, Ger. pat. 507,049 (*Chem. Zentr.*, 1932, II, 295).

³⁸ de Diesbach, Ger. pat. 511,210 (*Chem. Zentr.*, 1931, II, 2514).

³⁹ de Diesbach, Gubser, and Spoorenberg, *Helv. Chim. Acta*, **13**, 1265 (1930).

⁴⁰ de Diesbach, Wanger, and Stockalper, *Helv. Chim. Acta*, **14**, 355 (1931).

⁴¹ Einhorn, *Ann.*, **361**, 113 (1908).

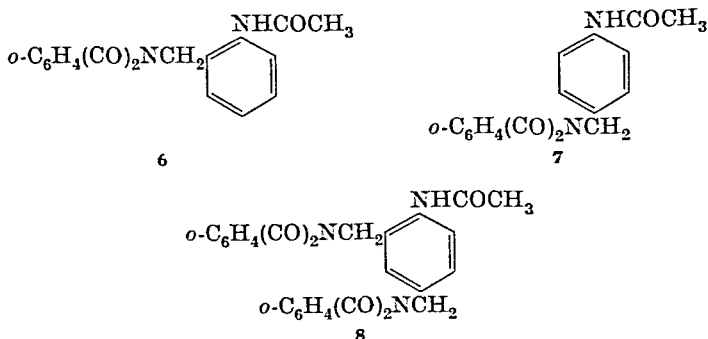
⁴² Einhorn, Ger. pat., 208,255 (*Chem. Zentr.*, 1909, I, 1281).

⁴³ Einhorn and Feibelman, *Ann.*, **361**, 140 (1908).

⁴⁴ Ota, Kaneyuki, and Matsui, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **81**, 1849 (1960).

[*C.A.*, **56**, 2373 (1962)].

6% and the disubstituted product 8 was isolated in 66% yield. Only a trace of 6 was obtained.



Similar results were observed with 4-methylacetanilide, but the activating effect of the methyl group in this substrate reduced the optimum sulfuric acid concentration to 97.7%. Under these conditions a mixture of the two possible monosubstitution products was formed in 78% yield. In 99.5% sulfuric acid only a 20% yield was obtained. That sulfonation as well as disubstitution played an important role in these experiments was demonstrated by the fact that, with acetanilide in 100% sulfuric acid, sulfonation occurred to the extent of 98% after 24 hours at room temperature, whereas, in 95% acid under the same conditions, sulfonation proceeded to the extent of 18%.

To minimize this undesirable property of sulfuric acid, other workers have used glacial acetic acid as a diluent.^{13,40,45,46} In another instance the condensation of N-methylolchloroacetamide with phenylacetic acid was allowed to proceed in anhydrous hydrogen fluoride.⁴⁷ Other means of avoiding the use of sulfuric acid in this reaction have failed, however. They include *p*-toluenesulfonic acid in benzene and anhydrous zinc chloride in phosphorus oxychloride.

Several other media, however, have been employed successfully in condensations of N-methylolamides. Unfortunately, the aromatic substrates employed generally possessed reactive ring systems. Thus it is not possible to deduce whether any of these media could be substituted for strong sulfuric acid (or anhydrous hydrogen fluoride) under all possible conditions. The most likely candidates appear to be polyphosphoric acid, anhydrous aluminum chloride, or boron trifluoride. Polyphosphoric acid and 100% phosphoric acid alone or in glacial acetic

⁴³ de Diesbach, Swiss pat. 136,046 (*Chem. Zentr.*, 1930, I, 3355).

⁴⁴ de Diesbach, Swiss pat. 139,642-139,645 (*Chem. Zentr.*, 1931, I, 2120).

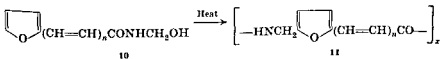
⁴⁵ Zaugg and Herrom, *J. Am. Chem. Soc.*, 80, 4317 (1958).

acid have brought about a few relatively easy amidomethylations,⁴⁸ and 85% phosphoric acid at 70–80° has effected the condensation of N-methylolacetamide with thiophene to give the amide **9** in yields of 50–60%.⁴⁹ Phosphorus pentoxide and phosphoric acid also have been used in the substitution of phthalocyanine dyes with N-methylolphthalimide.⁵⁰



Aluminum chloride in dry acetone or glacial acetic acid has been found to catalyze the reaction of a number of N-methylolamides with several phenols and phenol ethers in yields ranging from 60 to 73%.⁵¹ Although less reactive aromatic compounds were not included in this study, it was noted that the aluminum chloride-catalyzed reactions seemed to proceed faster than comparable ones in sulfuric acid. With boron trifluoride in benzene at 60°, N-methylol-N-methylacetamide gave the expected product, $\text{CH}_3\text{CON}(\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_5$, in 68% yield.⁵²

Several sets of mild conditions have been used for carrying out aromatic alkylations with N-methylolamides, but it is doubtful whether they possess any general advantages over the ethanolic hydrogen chloride method of Einhorn. A number of di- and tri-methoxybenzene derivatives⁵² and some phenolic dyes⁵³ have been successfully condensed with N-methylolamides by using anhydrous zinc chloride in acetic acid, but no yields were reported. Anhydrous formic acid at 50° sufficed to condense 2,4-xylenol with several N-methylolurea derivatives;⁵⁴ and merely heating the two N-methylolfuranamides **10** ($n = 0$ and 1) above their melting points generated the polymers **11** ($n = 0$ and 1).⁵⁵ However, heating in the absence of acid cannot be relied on to effect amidomethylation even of



⁴⁸ Arzneimittelfabrik Krewel-Leuffen, Austrian pat. 196,391 (1958) (*Chem. Zentr.*, 1960, 16521).

⁴⁹ Hartough, *Thiophene and Its Derivatives*, Interscience Division, John Wiley & Sons, New York, 1952, p. 253.

⁵⁰ American Cyanamid Co., Brit. pat. 695,523 [*C. A.*, 48, 1016 (1954)]

⁵¹ Arzneimittelfabrik Krewel-Leuffen, Austrian pat. 191,878 (1957) (*Chem. Zentr.*, 1958, 13359)

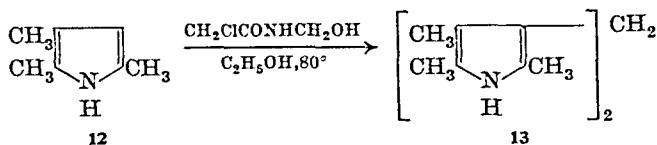
⁵² Monti and Verona, *Gazz. Chim. Ital.*, 60, 777 (1930) [*C. A.*, 25, 1225 (1931)].

⁵³ Haack, U.S. pat. 2,340,528 [*C. A.*, 38, 4385 (1944)]

⁵⁴ Zigeuner, Knerzinger, and Voglar, *Monatsh. Chem.*, 82, 847 (1951)

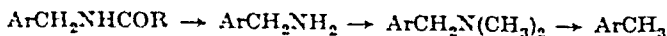
⁵⁵ Zigeuner, Voglar, and Pitter, *Monatsh. Chem.*, 85, 1196 (1954).

the most reactive aromatic systems. Thus heating the trimethylpyrrole 12 in ethanol at refluxing temperature with N-methylolchloroacetamide gave none of the expected amide. Only the dipyrromethane 13 was produced, presumably by reaction with formaldehyde derived in turn from cleavage of the N-methylolamide.¹⁷



Because of the unusually high reactivity of most methylolamides in strong sulfuric acid and the consequent reduction in selectivity of substitution, many aromatic amidomethylations are complicated by the production of mixtures of isomers and polysubstitution products. For this reason many derivatives formed from substitutions involving equivocal orientations have not yet been characterized adequately. In some instances only the structure of the most readily isolable product in the mixture has been determined. In a few other instances only half-hearted attempts have been made to resolve the mixture; and in still others, particularly where the Tscherniac-Einhorn reaction has been used to introduce basic auxochrome groups into certain aromatic dye structures, little effort to purify products is apparent. However, the modern methods of isolation and characterization that are now available to the organic chemist should serve to remove what has been a formidable barrier to progress in this area.

The characterization of those aromatic amidomethylation products not readily obtainable by independent synthesis has been accomplished in many ways. Perhaps the most common is the direct permanganate^{13,56} or dichromate⁵⁷ oxidation to a known carboxylic acid, $\text{ArCH}_2\text{NHCOR} \rightarrow \text{ArCO}_2\text{H}$. Another method involving two steps is hydrolysis to the benzylamine followed by conversion to a known hydroxymethyl derivative with nitrous acid, $\text{ArCH}_2\text{NHCOR} \rightarrow \text{ArCH}_2\text{NH}_2 \rightarrow \text{ArCH}_2\text{OH}$.⁵⁶ A three-step method which can be carried out with only one intervening isolation⁵⁷ involves methylation of the benzylamine and hydrogenolysis to a known methylated aromatic compound,⁴⁷

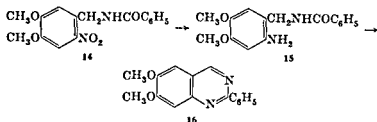


Amidomethylation occurring *ortho* to a functional group often can be diagnosed by subsequent cyclization, although completely unequivocal

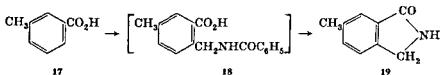
¹⁷ O'Connide, *Proc. Roy. Irish Acad.*, **42B**, 359 (1935) [*C.A.*, **29**, 7326 (1935)].

⁴⁷ Truitt and Creagh, *J. Org. Chem.*, **27**, 1065 (1962).

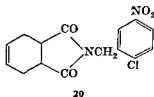
identification may not necessarily be achieved thereby. Thus reduction of the product 14 obtained by benzamidomethylation of 4-nitroveratrole gave an amine 15 which could be cyclized to the quinazoline 16 in the presence of phosphorus oxychloride.⁵⁸



As might be expected, *m*-toluic acid (17) underwent substitution *ortho* to the carboxyl group. The only product isolated (in unspecified yield) from its reaction with *N*-methylolbenzamide in concentrated sulfuric acid was 6-methylphthalimidine (19) resulting from intramolecular amide interchange of the initial product 18.⁷



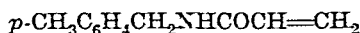
With Formaldehyde and Amides or Nitriles. Few reports of this modification of the Tscherniac-Einhorn reaction have appeared. Buc applied it to the condensation of lactams and imides with some aromatic nitro compounds, using concentrated sulfuric acid as the medium.³¹ Thus 4-chloronitrobenzene with equivalent amounts of paraformaldehyde and 4-cyclohexene-1,2-dicarboximide in concentrated sulfuric acid at 65° gave the monosubstitution product 20 in 75% yield.



Parris and Christenson used a series of aliphatic and aromatic nitriles, and even hydrogen cyanide, with paraformaldehyde in sulfuric-acetic acid mixtures at temperatures varying from ambient to 90°. Although yields ranged from 20 to 90% most of the aromatic compounds used were

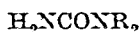
⁵⁸ Downes and Lions, *J. Am. Chem. Soc.*, **72**, 3053 (1950).

more reactive than benzene. Bromobenzene, however, with acetonitrile and formaldehyde in concentrated sulfuric acid gave the monosubstitution product $p\text{-BrC}_6\text{H}_4\text{CH}_2\text{NHCOCH}_3$ in 37% yield. In the reaction of acetonitrile and formaldehyde with *m*-xylene, 85% phosphoric acid at 90° gave a better yield (66% vs. 52%) than a sulfuric-acetic acid mixture at the same temperature. Of some interest is the successful utilization of acrylonitrile. With toluene and formaldehyde in a sulfuric-acetic acid mixture at room temperature it afforded the acrylamide



in 89% yield.

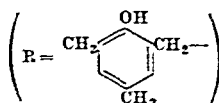
Surprisingly, even after heating a mixture of urea, formaldehyde, and 2,4-xylenol in formic acid at 50° for 2 hours, two monomeric urea derivatives **21** and **22** could be isolated.⁵⁹



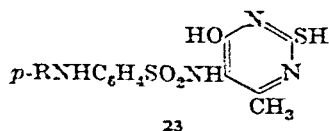
21



22



Extension of this reaction to sulfonamides also has been described.⁶⁰ Sulfanilamide and its *N*⁴-acetyl derivative were heated with formaldehyde and 4-methyl-2-thioiuracil in an acetic-hydrochloric acid mixture. The products were assigned structure **23** ($\text{R} = \text{H}$ and CH_3CO).

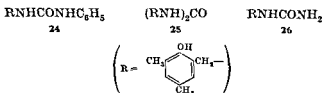


With Ethers of *N*-Methylol-amides and -imides. Most of the few reported examples of this condensation involve the diamidomethyl ethers, $(\text{RCONHCH}_2)_2\text{O}$, formed by self-condensation of corresponding methylol-amides. Thus in his original work Tscherniac was able to condense diphtalimidomethyl ether, $[o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2]_2\text{O}$, with phenol, 4-nitrophenol, and 2-nitrotoluene, using concentrated sulfuric acid.⁶¹ Zigeuner and co-workers studied the condensations of similar ethers derived from methylolureas.⁵⁴ With anhydrous formic acid at 50° , they obtained the

product **24** from the ether $(\text{C}_6\text{H}_5\text{NHCONHCH}_2)_2\text{O}$ and 2,4-xylenol in 90% yield. Under similar conditions the complex ether

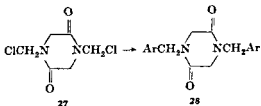


gave the disubstituted urea **25** as the main product together with small amounts of the mono- and tri-substituted ureas **26** and **22**, respectively.⁶²



Three reactions involving unsymmetrical ethers have been described. N-Ethoxymethylphthalimide in 100% sulfuric acid at 80–90° gave monosubstituted products with benzene (5% yield) and nitrobenzene (41% yield).⁶³ A disubstituted product of undetermined structure was obtained when copper phthalocyanine was treated with N-methoxymethylphthalimide in 100% sulfuric acid at 100°. ⁶⁴ The corresponding symmetrical diphtalimidomethyl ether at 75° in 100% acid reportedly gave only a monosubstituted derivative.⁵⁰

With N-Halomethyl-amides, -imides, and -carbonyl Compounds. Since its introduction by Cherbuliez and co-workers in 1922,^{65,66} this method of amidomethylation has seen comparatively little use. The original workers showed that both functions in 1,4-dichloromethyl-2,5-piperazinedione (**27**) attack naphthalene and 2-naphthol even in the absence of catalyst.⁶⁵ Merely heating the dione **27** with 2-naphthol in benzene under reflux gave **28** (Ar = 2-hydroxy-1-naphthyl) in 89% yield. Although the dichloromethyl derivative **27** was inert to benzene in carbon



⁶³ Zigeuner and Pitter, *Monatsh. Chem.*, **86**, 57 (1955).

⁶⁴ Tanimoto, Kyo, and Oda, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **65**, 1583 (1962) [*C. A.*, **59**, 505 (1963)].

⁶⁵ Rösch and Bayer, *Ger. pat.* 852,588 (*Chem. Zentr.*, 1953, 8213).

⁶⁶ Cherbuliez and Feer, *Helv. Chim. Acta*, **5**, 678 (1922).

⁶⁷ Cherbuliez and Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925).

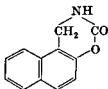
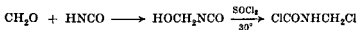
disulfide, addition of a catalytic amount of anhydrous aluminum chloride gave 1,4-dibenzyl-2,5-piperazinedione (28, $\text{Ar} = \text{C}_6\text{H}_5$) in 43% yield.⁶⁵ More recent work has extended the method to N-substituted N-chloromethylamides, $\text{RCON(R')CH}_2\text{Cl}$.^{32,67} Anhydrous aluminum chloride was the catalytic agent used in most of these studies.³²

Many of the N-halomethylamides are difficult to isolate and purify. Both N-chloro- and N-bromo-methylphthalimide are, however, fairly stable, but reactive, crystalline solids. For this reason they have been the reagents of choice ever since the former was first used by Herzberg and Lange in 1927.⁶⁸ As an example of their high reactivity, it was noted that, when a mixture of 4-chlorophenol, N-chloromethylphthalimide, and a trace of zinc chloride was warmed on the steam bath, spontaneous heating to 130° occurred and the product, 2-phthalimidomethyl-4-chlorophenol, was formed in 70% yield.⁶⁹ Similar exothermic behavior was observed in the reaction of N-bromomethylphthalimide with benzene.¹⁴ Indeed, this reagent proved sufficiently reactive to alkylate phenylacetic acid in the presence of zinc chloride catalyst.⁴⁷

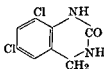
Utilization of the high reactivity of N-bromomethylphthalimide for the characterization of alcohols and phenols has been recommended twice.^{70,71} Unfortunately, both groups of workers assigned ether structures to their phenolic derivatives. Recent work has demonstrated, however, that reaction of N-bromomethylphthalimide with phenol under their conditions (no catalyst) gave a mixture of *o*- and *p*-phthalimidomethylphenols.¹⁵ No N-phenoxy-methylphthalimide could be detected in the reaction mixture. Undoubtedly the corresponding derivatives of the other phenols (thymol and β -naphthol) reported by these workers are likewise substituted in the aromatic nucleus.⁷¹

The N-halomethyl-amides and -imides represent the most strongly electrophilic reagents presently available for the amidomethylation reaction. Recently Olah and co-workers have been able to isolate stable oxocarbonium salts of very strong acids, e.g., $\text{RCO}^+ \text{SbCl}_6^-$.⁷² These are extremely efficient aromatic acylating agents and do not require the presence of Lewis acid catalysts. This suggests that, if a salt such as $\text{o-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{SbCl}_6^-$ could be isolated, i.e., by treatment of N-chloromethylphthalimide with antimony pentachloride, it might serve as a powerful amidomethylating reagent even in the absence of a polarizing catalyst.

A recently developed bifunctional reagent is chloromethylcarbamoyl chloride (29).⁷³ With β -naphthol in the absence of catalyst it gives 3,4-dihydro-2H-naphtho[1,2-*e*]-1,3-oxazin-2-one (30) in 25% yield. 2,4-Dichloroaniline gives the analogous nitrogen heterocycle, 3,4-dihydro-6,8-dichloro-2(1H)-quinazolinone (31). Less reactive aromatic compounds such as *m*-xylene require a zinc chloride catalyst. Chloromethyl isocyanate, ClCH_2NCO , readily obtainable from 29 can be used in its place in these reactions.



30



31

With *N,N'*-Methylene-, -Alkylidene- and -Arylidenebisamides. The diminished reactivity of these amide derivatives usually requires correspondingly increased reactivity of the nucleophiles. Hence, in the aromatic series, amidoalkylations of this type have usually been restricted to the activated systems: phenols, phenol ethers and esters, and anilides. Three methods have been used to effect condensation: heating the reactants at 190° ,⁷⁴ warming them at 50° in formic acid,⁵⁵ or treating them at 65 – 130° with phosphorus oxychloride alone or in chloroform.^{18,75–78} A single report, however, describes the extension of this reaction to benzene using 100% sulfuric acid as the condensing agent.⁶³

The formic acid method is probably the least general. Whereas 1,1'-methylenebis-(3-phenylurea), $(\text{C}_6\text{H}_5\text{NHCONH})_2\text{CH}_2$, and its *p*-tolyl analog gave with 2,4-xyleneol the unsymmetrical ureas 32,⁵⁵ neither *N,N'*-methylenebisbenzamide, $(\text{C}_6\text{H}_5\text{CONH})_2\text{CH}_2$,⁵⁵ nor *N,N'*-methylene-bisisovaleramide⁵⁴ underwent reaction under these conditions. On the

⁷³ Hoover, Stevenson, and Rothrock, *J. Org. Chem.*, **28**, 1825 (1963)

⁷⁴ Stefanović, Bojanović, Vandjel, Maksimović, and Mihailović, *Rec. Trav. Chim.*, **76**, 249 (1957).

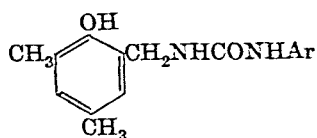
⁷⁵ Ishidate, Sekiya, and Yanaihara, *Chem. Pharm. Bull. (Tokyo)*, **8**, 1120 (1960) [*C.A.*, **57**, 9736 (1962)].

⁷⁶ Sekiya and Yanaihara, *Chem. Pharm. Bull. (Tokyo)*, **7**, 746 (1959) [*C.A.*, **54**, 16369 (1960)].

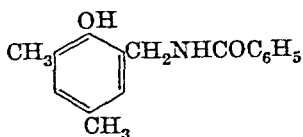
⁷⁷ Sekiya, Yanaihara, and Masui, *Chem. Pharm. Bull. (Tokyo)*, **9**, 945 (1961) [*C.A.*, **57**, 16459 (1962)].

⁷⁸ Sekiya, Yanaihara, and Masui, *Chem. Pharm. Bull. (Tokyo)*, **11**, 531 (1963) [*C.A.*, **59**, 8643 (1963)].

other hand, after only 1 hour at 95°, phosphorus oxychloride caused the

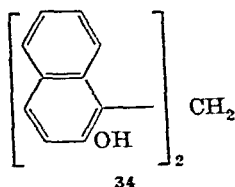


32 (Ar = C₆H₅ or *p*-CH₃C₆H₄)

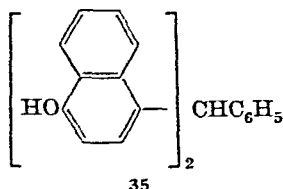


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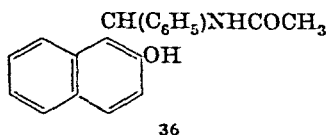
conversion of *N,N'*-methylenebisbenzamide and 2,4-xyleneol to the expected product 33 in 93% yield.⁷⁵ Dilute mineral acid catalysis appears to be useless in these reactions. Treatment of 2-naphthol with several methylenebisamides, (RCONH)₂CH₂, in ethanolic hydrochloric acid led to the methylenebisnaphthol 34 instead of the expected amidomethylation products.⁷⁹



34

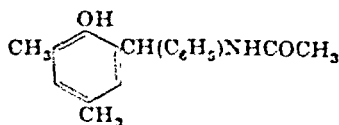


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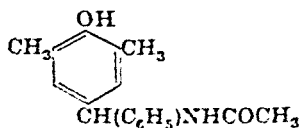


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A by-product, 35, of similar character was obtained when benzylidenebisacetamide, (CH₃CONH)₂CHC₆H₅, was heated 4 hours at 190° with 1-naphthol.⁷⁴ In contrast, 2-naphthol, under the same conditions, gave the α -amidoalkylation product, 36, in 93% yield.⁷⁴ This tendency for the thermal (190°) reaction to substitute *ortho* rather than *para* to the oxygen function is further supported by the observation that benzylidenebisacetamide with 2,4-xyleneol gave the *ortho* derivative 37 in 74% yield but the *para* isomer 38 from 2,6-xyleneol in 30% yield.⁷⁴ Furthermore, reactions of benzylidenebisacetamide and benzylidenebisbenzamide with phenol, phenyl acetate, and phenyl benzoate (all at 190°) led to *o*-mono-



37

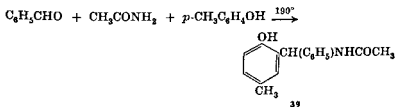


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amidoalkylated derivatives as the only isolable products, albeit in poor to moderate yields (12–69%).⁷⁴

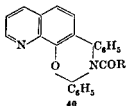
The phosphorus oxychloride method is less selective but considerably more effective in bringing about condensation. Thus treatment of phenol and *N,N'*-methylenebisacetamide with phosphorus oxychloride in chloroform for 4 hours under reflux gave a mixture of equal amounts of *o*- and *p*-acetamidomethylphenol.⁷⁷ By using various reaction temperatures and times, excellent yields were obtained from a number of other aromatic compounds. These included 4-nitrophenol (85%), 4-methoxytoluene (93%), and 2-methylacetanilide (86%).¹⁸ Other yields ranged from 71 to 98%.^{18,75}

The thermal (190°) condensation method was found not to require the preformed bisamide reagent.⁷⁴ Thus heating a mixture of benzaldehyde, acetamide, and *p*-cresol at 190° for 4 hours gave the alkylated product **39** in 58% yield. The use of preformed benzyldienebisacetamide gave a



lower yield, 43%. However, in most other instances the preformed reagent led to distinctly better yields.⁷⁴

Related to these amidoalkylations is an interesting condensation reported by Pirrone in 1937.⁸⁰ He found that 8-hydroxyquinoline treated with two equivalents of benzaldehyde and one of an amide (formamide, acetamide, benzamide, or salicylamide) in warm (60–80°) ethanol or benzene gave 3-acyl derivatives of 2,4-diphenyl-2-pyrido [3,2-*h*] [1,3]benzoxazine (**40**, R = H, CH₃, C₆H₅, or *o*-HOC₆H₄).



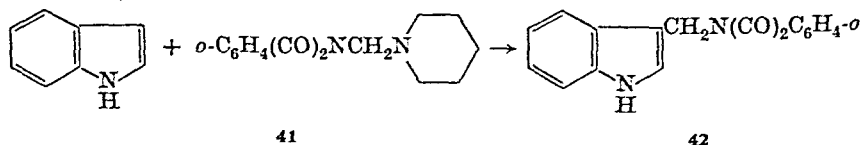
The use of an unsymmetrical methylene-bisamide has been reported once.⁶³ Treatment of benzene with *N*-benzamidoethylphthalimide in

⁸⁰ Pirrone, *Gazz. Chim. Ital.*, **67**, 529 (1937) [*Chem. Zentr.*, 1938, I, 1581] [*C.A.*, **32**, 1701 (1938)].

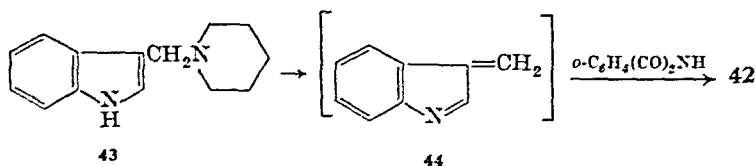
100% sulfuric acid at 90° gave N-benzylphthalimide in 24% yield. No N-benzylbenzamide was isolated.

With N-Aminomethyl-amides and -imides. Compounds of this type, e.g., $\text{RCON(R'')CH}_2\text{NR}_2'$, do not amidomethylate directly at a carbon atom of an aromatic system. Rather, they cleave as indicated $\text{RCON(R'')}-\text{CH}_2\text{NR}_2$ and thus behave as *aminomethylating agents*. A special reaction of indole is known, however, in which the end result is the same as if an amidomethylation had occurred.

When equivalent amounts of indole and N-piperidinomethylphthalimide (41) were heated under reflux for 9 hours in xylene containing a little powdered sodium hydroxide, 3-phthalimidomethylindole (42) was isolated in 48% yield.⁸¹ When the reaction was interrupted after 1-2 hours,

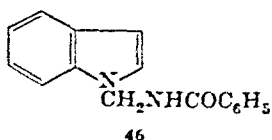
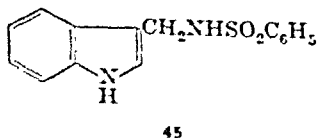


however, N-skatylpiperidine (43) was obtained in 50% yield. The latter compound was converted smoothly to 42 by further treatment with phthalimide. Thus the aminomethylation product 43 was formed first; but on prolonged treatment it reacted further with the phthalimide present, probably by an elimination-addition mechanism involving 44,



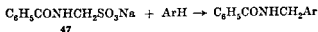
typical of alkylation reactions of gramine.

N-Piperidinomethylbenzenesulfonamide condensed with indole in the same way to give 45, but in only 21% yield.⁸² N-Dimethylaminomethylbenzamide, however, amidomethylated the nitrogen atom of indole.⁶³

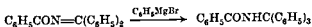


No further reaction could be induced, and the monosubstituted product 46 was isolated in 57% yield. Supposedly the methylene imide, $\text{CH}_2=\text{NCOC}_6\text{H}_5$, is the intermediate in this reaction and the NH group is the only function in indole sufficiently reactive to add to it. Attempts to force substitution at the 3-position of indole by using media acidic enough presumably to form the stronger electrophile $\text{CH}_2\text{NHCOC}_6\text{H}_5^+$ led only to decomposition of the acid-sensitive substrate.⁶³

With Amidomethanesulfonic Acids. Only two reactions of this type have been described.⁶³ Both involved the use of sodium benzamido-methanesulfonate (47) as the reagent. With benzene in 100% sulfuric acid at 95°, N-benzylbenzamide was isolated in 62% yield. With nitrobenzene under similar conditions N-(*m*-nitrobenzyl)benzamide was obtained, but in only 8% yield.



With N-Acylimines. Only one example of this type of reaction has been found. Ivanoff treated N-benzoyldiphenylketimine with phenylmagnesium bromide and obtained N-benzoyltritylamine in 62% yield.¹⁹



α -Amidoalkylation of Aliphatic Carbon Atoms

With N-Methylol and N- α -Alkylol Derivatives of Amides, Imides, and Carbamyl Compounds. The extension of the Tscherniac-Einhorn reaction to the aliphatic series is limited by the side reactions that aliphatic compounds undergo in strong acid media. The nucleophiles successfully employed possess active hydrogen atoms on aliphatic carbon atoms and would be expected to exhibit a wide range of nucleophilic activity.

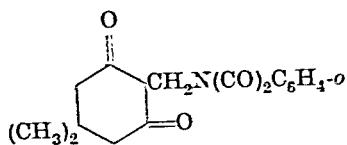
Several attempts to amidomethylate malonic ester with N-methylolbenzamide and N-methylolphthalimide in sulfuric acid have failed.^{64,65} Monti succeeded, however, in benzamidomethylating 1-phenylpropane-1,3-dione and 1,3-diphenylpropane-1,3-dione, although no yields were given.⁶⁶ Hellman and co-workers, using the same substrates as well as pentane-2,4-dione, 5,5-dimethylcyclohexane-1,3-dione, and 1,2-diphenylpyrazolidine-3,5-dione with N-methylolphthalimide in concentrated sulfuric acid, were able to prepare the amidomethylated products in about

⁶⁴ Buc, *J. Am. Chem. Soc.*, **69**, 254 (1947).

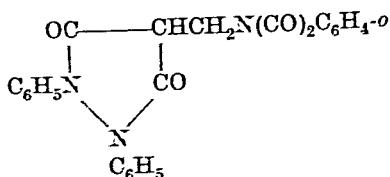
⁶⁵ Hellmann, Aichinger, and Wiedemann, *Ann.*, **626**, 35 (1959).

⁶⁶ Monti, *Gazz. Chim. Ital.*, **60**, 39 (1930) [*C.A.*, **24**, 4013 (1930)].

80% yields.⁸⁵ The alkylated derivatives 48 and 49 are examples of the products obtained.

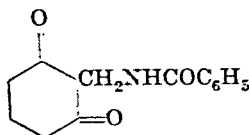


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The reaction conditions usually employed, i.e., concentrated sulfuric acid, do not seem to be generally applicable, although admittedly they have been studied only to a limited extent. The reaction of N-methylolbenzamide with cyclohexane-1,3-dione is reported to give the amido-methylated diketone 50 in 36% yield with concentrated sulfuric acid; in 20% yield with ethanol and hydrochloric acid; in 40% yield with acetic acid and zinc chloride; and in 65% yield with acetic acid and boron



50

trifluoride etherate.⁸⁵ By using boron trifluoride etherate, a 74% yield of the ketone $C_6H_5CONHCH_2CH(COC_6H_5)_2$ was obtained from the condensation of 1,3-diphenylpropane-1,3-dione with N-methylolbenzamide. The latter reaction conditions appear to provide a serviceable alternative to the use of concentrated sulfuric acid.

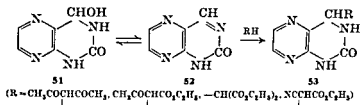
A series of reactions with trinitromethane as the nucleophile was carried out successfully using N-methylolurethan and a variety of N-methylolamides.^{87,88} An example is the reaction of trinitromethane with N-methylolmethacrylamide in water to give the amide



in 87% yield. Yields were not given for all the reactions, but those reported were above 80%. With these compounds water often served as the solvent, and the condensation occurred readily over a wide range of pH (<7).

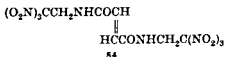
An interesting reaction has been reported in which 2-hydroxypteridine hydrate (51) was condensed with four different active methylene compounds (pentane-2,4-dione, ethyl acetoacetate, diethyl malonate, and

ethyl cyanoacetate) in 75, 80, 90, and 90% yields, respectively, to give compounds of structure **53**.⁸⁹ Since the reactions were conducted in



neutral or basic media, it is likely that they proceed by a Michael-type addition of enolate anion to the pteridine 52 rather than directly through the hydrate 51.

Only a few reactions of *N,N'*-dimethylol compounds have been reported.⁸⁷ *N,N'*-Dimethylolfumaramide and trinitromethane in water at pH 0.8 gave the fumaramide 54 in 48% yield. A patent describes the reaction of trinitromethane with *N,N'*-dimethylolurea and with a urea-



formaldehyde mixture to give $\text{CO}[\text{NHCH}_2\text{C}(\text{NO}_2)_3]_2$ in 77% and 88% yields, respectively.⁸⁸ The condensation of acetylene with $\text{N,N}'$ -dimethylolurea to give N -methylol- N' -2-propynylurea is mentioned.⁹⁰

With Formaldehyde or Acetaldehyde and Sulfonamides. Alkyl- and aryl-sulfonamides with formaldehyde and alkali cyanides give products of the type $\text{RSO}_2\text{NHCH}_2\text{CN}$. Reaction of benzenesulfonamide and acetaldehyde with potassium cyanide yields the analogous derivative, $\text{C}_6\text{H}_5\text{SO}_2\text{NHCH}(\text{CH}_3)\text{CN}$.⁹¹

Sulfanilamide and paraformaldehyde condense at elevated temperature with 2-picoline to give the product 55. Similar reactions occurred to give amidomethylated products from quinaldine, 9-methylacridine, 9-ethylacridine (i.e., 56), and 2-methyl-4(3*H*)-quinazolinone (i.e., 57).⁹² Indication that amidomethylation occurred on the methyl group of 2-methyl-4(3*H*)-quinazolinone and not on the amide nitrogen atom was

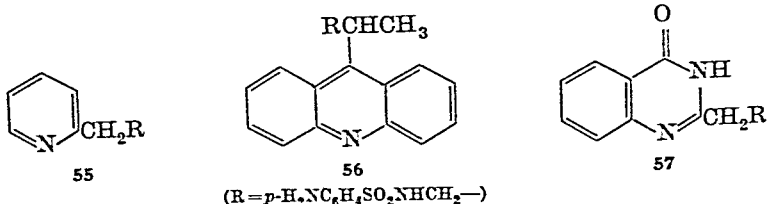
²² Albert and Howell, *J. Chem. Soc.*, 1962, 1591.

²² Reppe, Keyssner, and Hecht, Ger. pat. 724,759 [C.A., 37, 5733 (1943)]. Fr. pat. 839,875 (Chem. Zentr., 1939, II, 734).

⁵¹ Reuter, Ger. pat. 847,006 [*Chem.*, 50, 2689 (1956)].

²² Monti and Fehri, *Gazz. Chim. Ital.*, **70**, 375 (*Chem. Zentr.*, 1940, II, 2158).

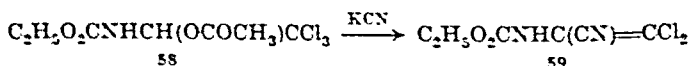
derived from the fact that no reaction took place with 4(3*H*)-quinazolinone, in which the 2-methyl group is absent. In contrast, *N*-methylolbenzamide



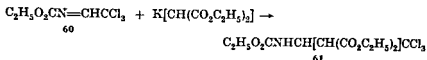
and 2-methyl-4(3*H*)-quinazolinone reportedly condense preferentially at the 3-nitrogen atom.^{92a}

With Ethers and Esters of *N*-Methylol- and *N*- α -Alkylol-amide Derivatives. Most of the reported work in this area is concerned with the reaction of trinitromethane with *N*-benzoxymethyl-acrylamide and -methacrylamide, CH₂=C(R)CONHCH₂OCOC₆H₅ (R = H, CH₃).⁹³ Both polar and non-polar solvents have been used with equally favorable results. Regardless of solvent, amidomethylation with the acrylamide derivative (R = H) occurred with concomitant addition of trinitromethane to the carbon-carbon double bond to produce the hexanitro compound (O₂N)₃CCH₂CH₂CONHCH₂C(NO₂)₃. That addition to the carbon-carbon double bond was faster than the ester cleavage was indicated by the observation that, with one equivalent of trinitromethane, the principal product was the adduct (O₂N)₃CCH₂CH₂CONHCH₂OCOC₆H₅. Trinitromethane did not add to the methacrylamide (R = CH₃). The same workers examined the reaction of trinitromethane with *N,N'*-diacetoxymethyl- and *N,N'*-dibenzoxymethyl-fumaramide and reported a 2% and 47% yield, respectively, of the product 54. Since water was the solvent for the reaction of the *N,N'*-diacetoxy compound, the formation of the fumaramide 54 may occur by a mechanism different from that involving the dibenzoate. The latter reaction was carried out under anhydrous conditions.

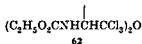
The trichloromethyl derivative 58 reacted with potassium cyanide to give the unsaturated nitrile 59 in 53% yield.⁹⁴ Elimination-substitution reactions of this type take place in a number of reactions with alkali cyanides. The reactions are described on pp. 82-83. In the same article it was reported that the unsaturated trichloromethyl derivative 60 and the



potassium salt of diethyl malonate gave the triethyl ester 61 in 35% yield. It was later shown, however, that 60 was actually the symmetrical



ether 62.⁹⁵ This reaction, therefore, appears to be the only one in which an ether has been utilized, albeit unknowingly, as an α -amidoalkylating agent of an aliphatic carbon atom.



With N-Halomethyl- and N- α -Haloalkyl-amide Derivatives. The N-halomethyl- or N- α -haloalkyl-amides are the reagents of choice for the amidoalkylation of aliphatic compounds,^{33,95-101} in contrast to the aromatic series where N-alkylolamides are more commonly employed. The halomethylamides often are prepared just before use and, with little or no purification, are added to the alkali metal derivative of the active methylene compound suspended in some inert solvent. Many structural types have been utilized. A partial list would include malonic esters and their monosubstituted derivatives, cyclic and acyclic β -diketones, cyanoacetic esters, acetoacetic esters and their monosubstituted derivatives, and nitroacetic ester. Reported yields exhibit wide ranges.

No systematic investigation of the important reaction conditions is available, but the N-halomethyl derivatives of aliphatic amides generally give lower yields than do N-halomethylbenzamides and N-halomethylphthalimides. For example, diethyl methylmalonate condenses with N-chloromethylformamide, with N-chloromethylacetamide, with N-chloromethylbenzamide, and with N-chloromethylphthalimide in 20, 31, 77, and 81% yields, respectively.^{97,100}

With N-chloro- and N-bromo-methylphthalimide, monosubstituted derivatives of active methylene compounds appear to react more smoothly than do unsubstituted ones. The amidomethylation product 63 was not obtained from N-bromomethylphthalimide and the sodium derivative of diethyl malonate in benzene. Instead, the tetra ester 64, phthalimide,

⁹⁵ Feist, *Ber.*, **45**, 945 (1912).

⁹⁶ Böhme, Broese, Dick, Eiden, and Schunemann, *Chem. Ber.*, **92**, 1599 (1959).

⁹⁷ Böhme, Broese, and Eiden, *Chem. Ber.*, **92**, 1258 (1959).

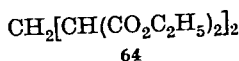
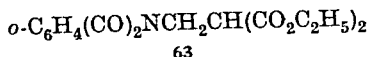
⁹⁸ Böhme, Dick, and Driesen, *Arch. Pharm.*, **294**, 312 (1961).

⁹⁹ Böhme and Eiden, *Arch. Pharm.*, **292**, 642 (1959).

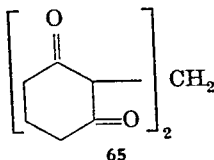
¹⁰⁰ Böhme and Eiden, *Ger. pat.* 1,025,883 [*C.A.*, **54**, 9773, (1960)].

¹⁰¹ Böhme, Eiden, and Schunemann, *Arch. Pharm.*, **294**, 307 (1961).

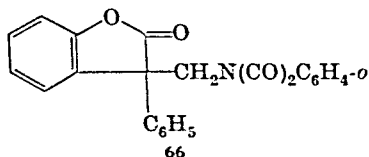
and sodium bromide were formed.¹⁰² This result is compatible with the



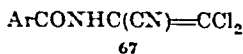
observation that phthalimide is cleaved from 2-phthalimidomethylcyclohexane-1,3-dione in the presence of excess active methylene compound to produce methylenebiscyclohexane-1,3-dione 65.¹⁰³ In both reactions it seems likely that a second molecule of the enolate ion displaces a phthalimide anion (e.g., from 63), giving the observed products.



Failure to obtain the normal substitution product from N-bromomethylphthalimide and sodioacetoacetic ester also has been reported.¹⁰⁴ In contrast, good yields have been obtained from the reaction of N-chloromethylphthalimide with the sodium derivatives of many *monosubstituted* active methylene compounds,⁹⁷ and the amidomethylated compound 66 has been prepared in 73% yield from N-bromomethylphthalimide and the sodium salt of 3-phenylbenzofuran-2-one.¹⁰⁵



An interesting set of reactions has been reported in which various substituted aromatic α -haloalkylamides of the type ArCONHCHClCCl_3 are treated in dry acetone with 2 moles of potassium cyanide to give, not the simple substitution products, but products of the type



¹⁰² Vinkler and Szabó, *Magy. Kem. Folyoirat*, **56**, 209 (1950) [*C.A.*, **45**, 7984 (1951)]; published in Russian in *Acta Chim. Hung.*, **1**, 103 (1951) [*C.A.*, **46**, 2500 (1952)].

¹⁰³ Hellmann and Aichinger, *Chem. Ber.*, **92**, 2122 (1959).

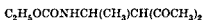
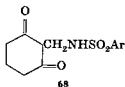
¹⁰⁴ Pucher and Johnson, *J. Am. Chem. Soc.*, **44**, 817 (1922).

¹⁰⁵ H. E. Zaugg and R. W. De Net, unpublished data.

in which elimination has occurred as well.^{106,107} One mole of potassium cyanide reacts rapidly, but no pure product can be isolated. Apparently the second mole of cyanide dehydrochlorinates the initially formed substitution products to the more readily isolable unsaturated nitriles 67. The yields of the nitriles 67 are only fair, but their hydrolysis to the corresponding acids can be achieved in essentially quantitative yields.

With N,N'-Methylenedisulfonamides and N,N'-Ethyldienebis-urethan or Their Precursors. Only a few successful reactions of this type have been described.^{85,108} In general, N,N'-alkylidenebisamides fail to undergo amidomethylation with active methylene compounds^{109,110} Instead they give the corresponding alkylidene derivatives, i.e., $RCH(CHX_2)_2$, analogous to the methylenebis compounds 64 and 65.

The condensation of cyclohexane-1,3-dione in sulfuric acid with N,N'-methylenedibenzenesulfonamide or N,N'-methylenedi-*p*-toluenesulfonamide yielded the corresponding diketones 68 in 18 and 19% yields, respectively.⁸⁵



69

Ethyl carbamate, acetaldehyde, and pentane-2,4-dione were condensed to give the urethan 69.¹⁰⁸ This is apparently the only reported case of amidoalkylation with an alkylidenebisamide derivative.

With N,N'-Arylidenebisamides or Their Precursors. The reactivity of these amide derivatives though diminished is still sufficient for condensation with most of the reactive methylene compounds. Two methods are generally used to effect the condensation: the preformed arylidenebisamide is condensed with the active methylene compound, or the aldehyde and amide (or the ammonium salt of the corresponding carboxylic acid) are treated with the active methylene compound. Both methods usually involve acetic anhydride or acetic acid-acetic anhydride mixtures as the solvent, although early workers used ethanol and hydrochloric acid.^{108,111}

¹⁰⁶ Hirwe and Deshpande, *Proc. Indian Acad., Sci.* **13A**, 277 (1941) [*C.A.*, **35**, 6250 (1941)]

¹⁰⁷ Hirwe and Rana, *J. Indian Chem. Soc.*, **17**, 481 (1940) [*C.A.*, **35**, 2130 (1941)]

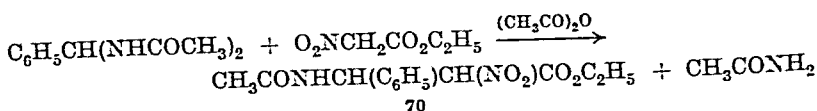
¹⁰⁸ Bianchi, *Gazz. Chim. Ital.*, **42** (I), 499 (1912) (*Chem. Zentr.*, **1912**, II, 329).

¹⁰⁹ Stefanović, Prekajski, and Mihailović, *Ber. Chem. Ges. Belgrade*, **22**, 113 (1937) (*Chem. Zentr.*, **1939**, 9883).

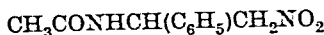
¹¹⁰ Stefanović, Stefanović, and Milanović, *Ber. Chem. Ges. Belgrade*, **20**, 313 (1935) (*Chem. Zentr.*, **1937**, 6134).

¹¹¹ Bianchi and Schiff, *Gazz. Chim. Ital.*, **41** (II), 81 (1911) (*Chem. Zentr.*, **1911**, II, 1919).

The condensation of arylidenebisamides with ethyl nitroacetate clarified the reaction course. It was shown that, when a mixture of benzaldehyde, acetamide, and ethyl nitroacetate in acetic anhydride was heated, the ester **70** was obtained in 61% yield.¹¹² The course of the reaction was the same when *N,N'*-benzylidenebisacetamide was substituted for the benzaldehyde and acetamide. Under the latter conditions, however, a better yield (85%) of **70** was obtained.



N,N'-Benzylidenebisacetamide also condensed with nitromethane in analogous fashion, producing the nitro compound



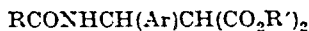
in 32% yield.¹¹³ As expected, nitromethane is less reactive than ethyl nitroacetate and requires a longer reaction time even for lower yields.

Ethyl acetoacetate has been condensed with aldehydes and amides in ethanol and hydrochloric acid¹¹¹ as well as with *N,N'*-arylidenebisamides in acetic anhydride.¹¹⁴ Compounds of the type



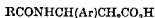
are obtained. Like acetoacetic ester itself, the condensation products exist in two tautomeric forms. As a consequence, they decolorize bromine water and produce a reddish brown coloration with alcoholic ferric chloride solution. Acid cleavage leads to β -aryl- β -acylaminopropionic acids, $\text{RCONHCH}(\text{Ar})\text{CH}_2\text{CO}_2\text{H}$, in good yields, but ketone cleavage does not occur.

The reaction of arylidenebisamides with malonic esters in acetic anhydride yields the expected condensation products.¹¹⁵



The reaction time appears to be important. For example, *N,N'*-benzylidenebisacetamide gives a 62% yield of amidoalkylated product in 3 hours, but after 9 hours only an 11% yield can be obtained. The major products isolated from these prolonged reactions are the arylidenemalonic esters $\text{ArCH}=\text{C}(\text{CO}_2\text{R}')_2$ resulting from the elimination of amide. Partial

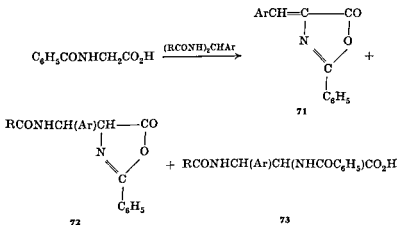
hydrolysis of the amidoalkylated esters produces the malonic acids which decarboxylate to give β -aryl- β -acylamino propionic acids



in excellent yields.¹¹⁵ Diethyl ethylmalonate reacts with N,N' -benzylidenebisacetamide in an analogous fashion. Although partial hydrolysis of the product leads to a half-ester of malonic acid, more severe conditions result in both decarboxylation and amide elimination to give α -ethylcinnamic acid, $\text{C}_6\text{H}_5\text{CH}=\text{C}(\text{C}_2\text{H}_5)\text{CO}_2\text{H}$.¹¹⁵

Reactions of cyanoacetic esters with arylidenebisamides do not take the expected course but lead to the elimination products $\text{ArCH}=\text{C}(\text{CN})\text{CO}_2\text{R}$.¹¹⁶ These condensations proceed best in the absence of any solvent or catalyst.

Hippuric acid as an active methylene compound condenses with arylidenebisamides in glacial acetic acid or in acetic anhydride to give, as the main product, β -aryl- α,β -diacylamino propionic acids, **73**, in two diastereomeric forms.¹¹⁷ In several reactions the corresponding azlactones **72** are formed; and in all instances small amounts ($\sim 10\%$) of the

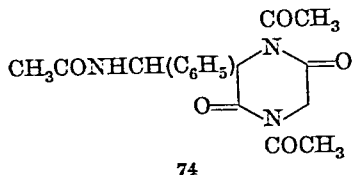


azlactones **71** of β -arylacrylic acids are obtained. The complicated configurational relationships among these products have not been completely elucidated. Hippuric acid does not react with *o*- or *p*-nitrobenzylidenebisacetamide, but the *meta* isomer gives the corresponding azlactone **71** ($\text{Ar} = m\text{-O}_2\text{NC}_6\text{H}_4$).¹¹⁷ The acids **73** as well as the azlactones **72** undergo acid hydrolysis to the corresponding β -aryl- α,β -diamino propionic acids, $\text{ArCH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$.

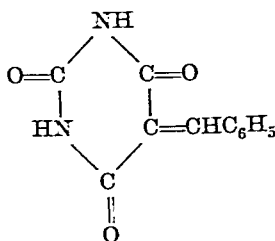
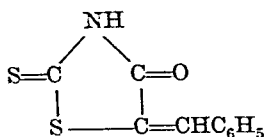
¹¹⁵ Stefanović and Nikić, *J. Org. Chem.*, **17**, 1305 (1952).

¹¹⁷ Stefanović and Stefanović, *J. Org. Chem.*, **21**, 161 (1956).

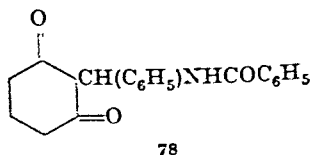
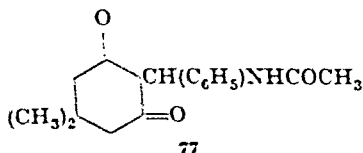
One heterocyclic compound which has been reported¹⁰⁹ to undergo reaction in acetic anhydride with *N,N'*-benzylidenebisacetamide is piperazine-2,5-dione. It gives the diketone **74** in 29% yield. Other heterocyclic compounds apparently condense with *N,N'*-benzylidenebis-



acetamide in glacial acetic acid but without leading to α -amidoalkylation products.^{109,110} Thus rhodanine gives **75** in 99% yield,¹¹⁰ and barbituric acid gives **76** in 91% yield.¹⁰⁹ The yield of the latter is lowered to 51% when the solvent is acetic anhydride.



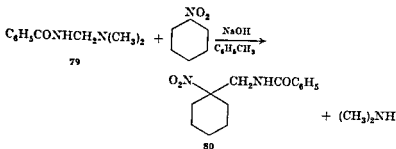
Some cyclic β -diketones are reported to condense with *N,N'*-benzylidenebisamides to give the corresponding 2-(α -acylaminobenzyl) derivatives in poor to moderate yields.⁸⁵ For example, 5,5-dimethylcyclohexane-1,3-dione, with *N,N'*-benzylidenebisacetamide, produces **77** in 12% yield. In the same manner cyclohexane-1,3-dione and *N,N'*-benzylidenebisbenzamide give the corresponding product **78** in 40% yield.



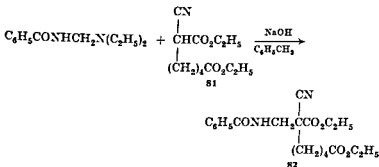
With *N*-Aminomethylamides and Their Quaternary Salts. In contrast to the aromatic systems, a number of reactive methylene compounds undergo base-catalyzed amidomethylation with *N*-dialkylaminomethylamides.^{61,115} They include dialkyl malonates and their

¹¹⁰ Hellmann and Haas, *Chem. Ber.*, **90**, 1357 (1957).

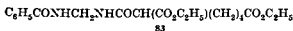
monosubstituted derivatives, ethyl acetoacetate, β-diketones, and nitrocyclohexane. For example, the last compound condenses with *N*-(di-methylaminomethyl)benzamide 79 in the presence of powdered sodium hydroxide in boiling toluene to give 80 in 38% yield.¹¹⁸



Two cyano compounds have been amidoalkylated by *N*-diethylamino-methylbenzamide with good results.¹¹⁸ Diethyl α-cyanopimelate (81) reacts in the expected manner to give an 85% yield of the product 82, and ethyl α-phenylcyanoacetate undergoes analogous conversion in 74%



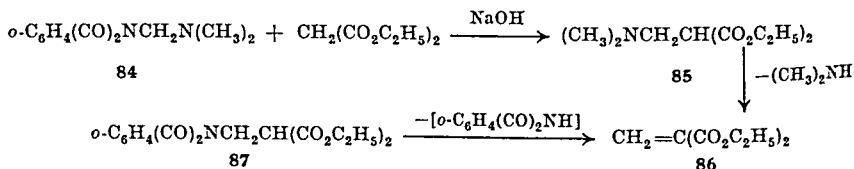
yield. In interesting contrast, however, is the observation that compound 81 with *N*-methylolbenzamide in strong acid is converted to the *N*-alkylated product 83 in high yield.^{84,119}



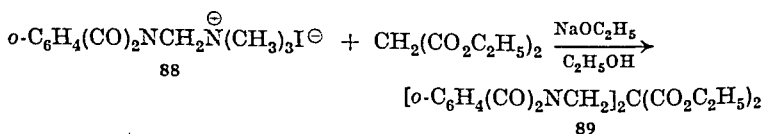
Only a few reactions of *N*-dialkylaminomethylphthalimides with reactive methylene compounds have been reported, and they have usually led to by-products.⁸¹ Diethyl malonate reacts with *N*-dimethylaminomethylphthalimide (84) to yield the unstable derivative 85. The chief products formed were phthalimide and diethyl methylenemalonate (86). Attempts to add phthalimide to 86 to produce 87 were not successful.

¹¹⁸ English and Clapp, *J. Am. Chem. Soc.*, 67, 2262 (1945).

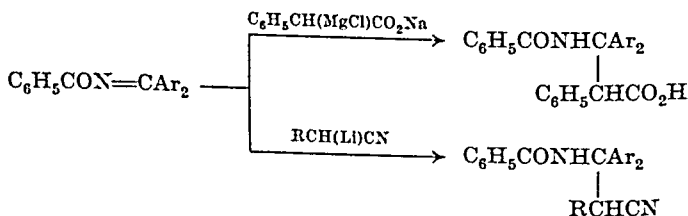
On the contrary, evidence indicated that, under the reaction conditions, 87, like 85, undergoes elimination to give 86.



The quaternary salt 88 reacted with diethyl malonate to give only a small amount of the dialkylated product 89.⁸¹ With sodium cyanide, however, it gave the nitrile *o*-C₆H₄(CO)₂NCH₂CN in 80% yield.



With N-Acylimines. Relatively few examples of this reaction have been reported. Ivanoff found that benzoyl derivatives of diaryl ketimines will add reactive nucleophilic agents such as the chloromagnesium derivative of sodium phenylacetate¹⁹ and the lithium derivatives of acetonitrile,¹²⁰ propionitrile,¹²¹ and butyronitrile¹²¹ prepared *in situ* with lithium amide in liquid ammonia.



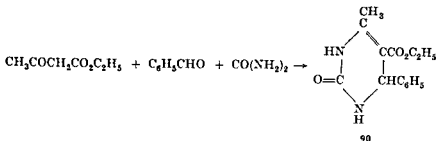
Yields of the reactions ranged between 40 and 85%. This synthesis offers promise as a convenient entry to systems highly substituted by bulky groups.

α-Amidoalkylation of Ethyl Acetoacetate with N,N'-Alkylidene- and N,N'-Arylidene-bisureas or Their Precursors. The Biginelli Pyrimidine Synthesis. Biginelli treated ethyl acetoacetate with urea

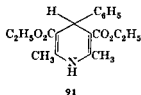
¹²⁰ Ivanoff, Markov, and Dohrev, *Compt. Rend. Acad. Bulgare Sci.*, **15**, 403 (1962) [C.A., **60**, 4112 (1964)].

¹²¹ Ivanoff, Konstantinova, and Popandova, *Compt. Rend. Acad. Bulgare Sci.*, **15**, 617 (1962) [C.A., **59**, 2689 (1963)].

and benzaldehyde and obtained 5-carbethoxy-2-keto-6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidine (90).¹²² He extended the reaction to other



aldehydes and made the first contribution to an understanding of the course of the reaction by using the corresponding arylidenebisureas, $(\text{H}_2\text{NCONH})_2\text{CHAr}$, in place of the aldehydes and urea.¹²²⁻¹²⁴ Under the original conditions the reaction gave only moderate yields, but later workers, by using a 1-mole excess of ethyl acetoacetate, were able to increase the yields appreciably.¹²⁵ Using benzaldehyde, they also showed that the substituted dihydrolutidine 91 was a by-product and that the



course of the synthesis can be described as follows. Preformed $\text{N,N}'$ -benzylidenebisurea reacts with ethyl acetoacetate to give 90. The molecule of urea which is eliminated in this process condenses with a second molecule of ethyl acetoacetate to give ethyl β -ureidocrotonate, $\text{CH}_3\text{C}(\text{NHCONH}_2)=\text{CHCO}_2\text{C}_2\text{H}_5$, which in turn reacts with benzaldehyde to give the Biginelli product 90. However, some of the ureidocrotonate hydrolyzes to ethyl β -aminocrotonate, ammonia, and carbon dioxide. In the presence of ammonia, conditions become favorable for the Hantzsch synthesis and this accounts for the side reaction leading to the pyridine derivative 91.

Further work confirmed these results and showed (a) that condensation of urea with ethyl α -benzylideneacetoacetate plays no part in the reaction; and (b) that under the reaction conditions the ureidocrotonate is partially

¹²² Biginelli, *Ber.*, **24**, 1317 (1891).

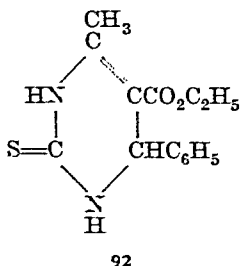
¹²³ Biginelli, *Ber.*, **24**, 2962 (1891).

¹²⁴ Biginelli, *Gazz. Chim. Ital.*, **23** (1), 360 (1893); *Ber.*, **26**, 447 (1893).

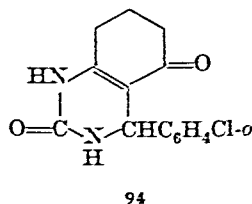
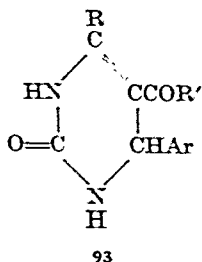
¹²⁵ Hunkel and Hey, *Rec. Trav. Chim.*, **48**, 1280 (1929).

cleaved to urea and ethyl acetoacetate.^{126,127} It was also demonstrated that the Biginelli synthesis is catalyzed by mineral acid, to which the yield is approximately proportional. In the absence of acid, reaction proceeds extremely slowly.

Thiourea can be substituted for urea in this process. With benzaldehyde the thiopyrimidine **92** is formed.¹²⁵



α -Amidoalkylation of Active Methylene Compounds Other than Ethyl Acetoacetate with Urea and Aldehydes. Some interesting work using aromatic aldehydes, urea, and β -diketones in acidic media has led to compounds of the type **93**.^{128,129} Nine aromatic aldehydes were used successfully with pentane-2,4-dione ($R = R' = \text{CH}_3$), and five



aromatic aldehydes were employed with 1-phenylbutane-1,3-dione. The yields were fair (40–90%), but the positions of the substituents in the butanedione products were not established. Propionaldehyde and urea react with pentane-2,4-dione in an analogous fashion (32% yield), but heptanal and isovaleraldehyde do not.

Cyclohexane-1,3-dione reacts with *o*-chlorobenzaldehyde and urea to give the bicyclic compound **94** in 80% yield.¹³⁰ The reaction is not general.

¹²⁶ Folkers, Harwood, and Johnson, *J. Am. Chem. Soc.*, **54**, 3751 (1932).

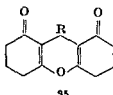
¹²⁷ Folkers and Johnson, *J. Am. Chem. Soc.*, **55**, 3784 (1933).

¹²⁸ Chi and Ling, *Acta Chim. Sinica*, **22**, 177 (1955); *Sci. Sinica*, **6**, 247 (1957) [*C.A.*, **52**, 356 (1958)].

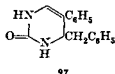
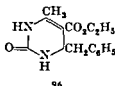
¹²⁹ Chi and Wu, *Acta Chim. Sinica*, **22**, 184 (1955) [*C.A.*, **52**, 6360 (1958)].

¹³⁰ Chi and Wu, *Acta Chim. Sinica*, **22**, 185 (1955) [*C.A.*, **52**, 6360 (1958)].

n-Butyraldehyde, *p*-methoxybenzaldehyde, and *p*-dimethylaminobenzaldehyde all condensed preferentially with 2 molecules of the diketone to give, after intramolecular dehydration, tricyclic compounds of type 95.

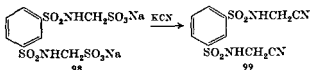


Phenylacetaldehyde did not yield the expected Biginelli product 96. Instead the pyrimidine 97 was obtained.¹³¹ Clearly this arises from the substitution of a molecule of phenylacetaldehyde for the usual ethyl acetoacetate. The same pyrimidine, 97, as expected, was also formed



when phenylacetaldehyde and urea were condensed in the absence of acetoacetic ester.

Amidomethylation of Potassium Cyanide with Arenesulfonamidomethanesulfonates. Only one report concerning arenesulfonamidomethanesulfonates seems to have appeared in the literature.¹³² The sulfonate 98, prepared by heating *m*-benzenedisulfonamide with sodium hydroxymethanesulfonate, on treatment with excess aqueous



potassium cyanide produced the dinitrile 99 in 75% yield. The nitrile is readily hydrolyzed to the corresponding dicarboxylic acid. The reaction with benzenesulfonamide proceeds in an analogous fashion.

Preparation of the Electrophilic Reagents

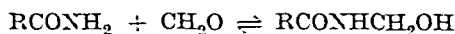
If there is any process within the scope of this review which has received adequate attention, it is the reaction of formaldehyde with cyclic and

¹³¹ Folkers and Johnson, *J. Am. Chem. Soc.*, **55**, 3361 (1933).

¹³² Knoevenagel and Lebach, *Ber.*, **37**, 4094 (1904).

acyclic mono- and poly-amides.¹³³ Studies of this reaction have involved the labeling of proteins and peptides,⁷⁹ the modification of nylon polymers,^{134,135} the preparation of cross-linking agents for crease-proofing or softening cotton textiles,^{136,137} and the development of waterproofing agents for textile materials.¹³⁸⁻¹⁴⁰ Furthermore the commercial importance of urea-formaldehyde and urea-acetaldehyde¹⁴¹ polymers has stimulated a number of fundamental investigations in this area.¹⁴²⁻¹⁴⁹

N-Methylol-amides and -imides. Amides and imides react reversibly with formaldehyde in acid, neutral, or basic media. The



reaction is catalyzed by either acid or base,¹⁴⁸ but, over a relatively wide pH range (2-12), the activation energy of the reverse reaction remains greater than that of the forward process by a nearly constant amount (~ 5 kcal./mole).^{144,145,149} Although the equilibrium favoring the N-methylolamide is practically unaffected by pH, elevated temperatures tend to favor the dissociation reaction which has the higher activation energy. For this reason the isolation of products often must be carried out at or near room temperature,^{35,84,150} and purifications by recrystallization should be conducted with a minimum of heating.^{151,152} In the absence of large concentrations of formaldehyde, contact with aqueous acid or alkali, as expected, causes reversal of the methylation reaction even at room temperature.⁷⁹

Condensation of amides with formaldehyde under neutral or basic conditions is preferred because acid catalysis often leads to further

¹³³ Walker, *Formaldehyde*, 2nd ed., Reinhold, New York, 1953, pp. 290-309.

¹³⁴ Cairns, Foster, Larchar, Schneider, and Schreiber, *J. Am. Chem. Soc.*, **71**, 651 (1949).

¹³⁵ Cairns, Gray, Schneider, and Schreiber, *J. Am. Chem. Soc.*, **71**, 655 (1949).

¹³⁶ Tovey, *Textile Res. J.*, **31**, 185 (1961) [*C.A.*, **55**, 11859 (1961)].

transformation of the N-methylolamides to the corresponding ethers, $(RCONHCH_2)_2O$, or methylenebisamides, $(RCONH)_2CH_2$. Kinetic studies indicate that the base-catalyzed reactions occur by attack of the amide anion, $RC(=NH)O^\ominus \leftrightarrow RC(=O)NH^\ominus$, at the carbonyl carbon atom of formaldehyde.^{132,133} This finding explains why reactivity toward formaldehyde under these conditions generally follows the order of increasing amide acidity, e.g.,



Early work indicated that susceptibility to N-methylolation by formaldehyde was generally restricted to primary amides.⁴¹ The monomethylol derivative of 1,3-dimethylurea¹⁵³ and three derivatives of the type $RCON(CH_2OH)_2$ ^{41,42} were originally the sole exceptions to this rule. Recent work, however, has demonstrated that the reactivity of N-mono-alkylated amides toward formaldehyde is greater than had been supposed.^{32,154,154a} Although the reaction may not be complete and products may not be readily isolable in crystalline form, many N-methylol-N-alkylamides can be obtained in good yields as crude oils and can be used in that form.

Unsubstituted^{155,156} and N-monosubstituted sulfonamides¹⁵⁷ also react readily with formaldehyde to give the N-methylol derivatives. Indications are, however, that they tend to disproportionate to the methylenebisamides and also undergo polymerization more readily than their carboxamide analogs.¹⁵⁶

N- α -Alkylolamides. Most aliphatic and all aromatic aldehydes do not behave toward amides as formaldehyde does. Reaction usually does not stop at the N-alkylol stage, $RCONHCHOHR'$, but progresses further to the alkylidene- or arylidene-bisamide, $(RCONH)_2CHR'$. 1-Ethylol- and 1,3-diethylol-urea have been prepared in crude form from acetaldehyde and urea, but, aside from these, the only exceptions to the rule above are the α -halogenated aldehydes.¹⁴¹ Chloral, for example, reacts readily with amides, either spontaneously or on heating with or without an acid catalyst, to give the N-alkylolamides, $RCONHCHOHCCl_3$, or "chloral-amides".¹³³ Sulfonamides also react readily.¹⁵⁹ Other aldehydes that

¹³³ Einhorn and Hamburger, *Ann.*, **361**, 122 (1908).

¹³⁴ Vail, Moran, and Moore, *J. Org. Chem.*, **27**, 2067 (1962).

^{134a} Chupp and Speziale, *J. Org. Chem.*, **28**, 2592 (1963).

¹³⁵ Feibelmann, Ger. pat. 403,718 (*Chem. Zentr.*, 1925, I, 440).

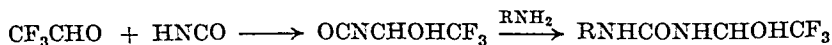
¹³⁶ Hug, *Bull. Soc. Chim. France*, 1934, 990.

¹³⁷ Wiedemann and Straasberger, Ger. pat. 947,795 [*C.A.*, **53**, 2262 (1959)].

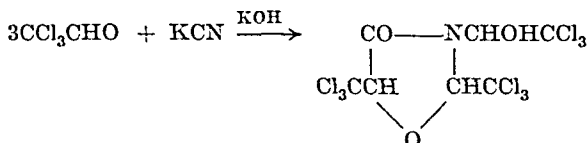
¹³⁸ Jacobson, *Ann.*, **157**, 245 (1871).

¹³⁹ Lichtenberger, Fleury, and Barette, *Bull. Soc. Chim. France*, 1955, 669.

have been shown to undergo the same condensation are bromal, bromo-dichloroacetaldehyde, dichloroacetaldehyde, dibromoacetaldehyde, and 2,2,3-trichlorobutanol. Numerous examples of these alkylolamides have been reported by Feist^{95,160} and by groups led by Chattaway,¹⁶¹⁻¹⁶³ Meldrum,¹⁶⁴⁻¹⁶⁷ and Hirwe.¹⁶⁸⁻¹⁷¹ Through 1962, however, extension of the reaction to the presently available trifluoroacetaldehyde apparently had not been reported. Also, one might expect some of the recently accessible polyfluorinated ketones to react analogously, especially in view of a recent report showing that carbamyl derivatives of fluorinated aldehydes and ketones are stable.⁷³ In this instance, however, they were prepared by the action of an alcohol or an amine on an intermediate isocyanate. A number of fluoral carbamates and ureas were prepared in this way.



Of incidental interest is another recent report showing that chloral reacts with potassium cyanide or chloral cyanohydrin in aqueous alkali to give a chloral-oxazolidone derivative.¹⁷²



As expected, these N-alkylolamides, like N-methylolamides, are unstable. On being warmed in water or heated above the melting point, they dissociate to amide and aldehyde.^{171,173} In alkaline media this occurs at room temperature.¹⁷¹ Hirwe and Rana have studied the effect

¹⁶⁰ Feist, *Ber.*, **47**, 1173 (1914).

¹⁶¹ Chattaway and James, *Proc. Roy. Soc. (London)*, **A134**, 372 (1931) [*C.A.*, **26**, 1249 (1932)].

¹⁶² Chattaway and James, *Proc. Roy. Soc. (London)*, **A137**, 481 (1932) [*C.A.*, **26**, 5549 (1932)].

¹⁶³ Chattaway and James, *J. Chem. Soc.*, 1934, 109.

¹⁶⁴ Meldrum and Bhojraj, *J. Indian Chem. Soc.*, **13**, 185 (1936) [*C.A.*, **30**, 5940 (1936)].

¹⁶⁵ Meldrum and Tata, *J. Univ. Bombay*, **6**, Pt. II, 120 (1937) [*C.A.*, **32**, 3761 (1938)].

¹⁶⁶ Meldrum and Deodhar, *J. Indian Chem. Soc.*, **11**, 529 (1934) [*C.A.*, **29**, 136 (1935)].

¹⁶⁷ Meldrum and Pandya, *J. Univ. Bombay*, **6**, Pt. II, 114 (1937) [*C.A.*, **32**, 3760 (1938)].

¹⁶⁸ Hirwe and Deshpande, *Proc. Indian Acad. Sci.*, **13A**, 275 (1941) [*C.A.*, **35**, 6250 (1941)].

¹⁶⁹ Hirwe, Gavankar, and Patil, *Proc. Indian Acad. Sci.*, **11A**, 512 (1940) [*C.A.*, **34**, 7882 (1940)].

¹⁷⁰ Hirwe and Kulkarni, *Proc. Indian Acad. Sci.*, **13A**, 49 (1941) [*C.A.*, **35**, 5502 (1941)].

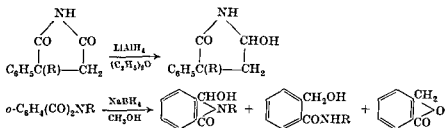
¹⁷¹ Hirwe and Rana, *Ber.*, **72**, 1346 (1939).

¹⁷² Bowman, Campbell, and Tanner, *J. Chem. Soc.*, 1963, 692.

¹⁷³ Bischoff, *Ber.*, **7**, 628 (1874).

of ring substitution on the ease of formation and stability of the *N*-alkylolamides, ArCONHCHOHCl_3 , derived from chloral and aromatic amides.¹⁷¹ Some of their findings are unusual and may be of some theoretical interest.

Cyclic *N*- α -alkylolamides are formed by hydride reduction of certain dicarboxylic imides. α,α -Disubstituted succinimides and glutarimides are reduced by lithium aluminum hydride at the unhindered carbonyl group.¹⁷⁴ Similarly, phthalimides can be reduced selectively with sodium borohydride.¹⁷⁵ Phthalide and *o*-hydroxymethylbenzamides often appear as by-products, however.



Only one α -alkylolamide appears to have been used directly for the alkylation of a carbon atom.⁸⁹ It is 2-hydroxypteridine hydrate (51; see p. 79), prepared by the condensation of 2-hydroxy-4,5-diaminopyrimidine with glyoxal in aqueous solution.¹⁷⁶ The more common chloralamides have not been employed as α -amidoalkylating reagents. Instead they have been converted to the more reactive halides, RCONHCHXCl_3 , with which successful alkylation is more likely.

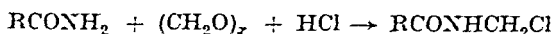
***N*-Halomethyl- and *N*- α -Haloalkyl-amides and -imides.** *A. N-Halomethyl Derivatives.* Most *N*-chloro- or *N*-bromo-methylamides or -imides have been prepared by treatment of the corresponding *N*-methylol derivatives with the reagents usually employed for making acid halides from carboxylic acids. Thionyl chloride alone,¹⁷⁷⁻¹⁸⁰ in ether,^{181,182} in chloroform,¹⁸³ or in benzene¹⁸⁴ provides the most generally convenient reagent for this transformation. However, phosphorus pentachloride or

pentabromide alone,¹⁸⁵ in ether,^{33,97,99,100,186} in chloroform,^{66,187} in a carbon tetrachloride-acetyl chloride mixture,⁶⁵ or in dioxane^{32,33} have often been used. Phosphorus trichloride or tribromide has also seen occasional service.^{8,188,189}

Phosphorus oxychloride has been effective in one instance.¹⁵¹ Although N-methylolphthalimide on short treatment gave only the symmetrical ether [*o*-C₆H₄(CO)₂NCH₂]₂O, prolonged heating at reflux temperature converted the ether to N-chloromethylphthalimide. N-Chloromethylphthalimide is also obtainable by warming N-ethoxymethylphthalimide¹⁹⁰ or N-piperidinomethylphthalimide¹⁹¹ with acetyl chloride.

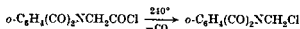
Certain N-methylolamides can be converted to the halides merely by heating in concentrated hydrochloric or hydrobromic acid.^{104,185,192-194} This reaction is not general, for, although N-chloromethylphthalimide can be prepared in this way,¹⁹² N-chloromethylmaleimide cannot.⁸ Concentrated sulfuric acid catalyzes the reaction of N-methylolphthalimide with 48% hydrobromic acid.^{70,104}

A number of N-chloromethylamides, particularly those derived from fatty acids, have been prepared directly from the amides by treatment with paraformaldehyde and dry hydrogen chloride in an inert solvent such as methylene chloride,¹⁹⁵ benzene,¹⁹⁶⁻²⁰⁰ dioxane,²⁰¹ or glacial acetic acid.^{202,203} The products were not isolated but were used directly without

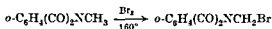


purification. Analyses of the crude mixtures indicated conversions of the order of 20 to 30%. Crude N-chloromethylbenzenesulfonamide, C₆H₅SO₂NHCH₂Cl, was also prepared in this way.²⁰¹

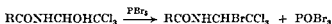
Two special methods have been utilized to prepare N-chloro- and N-bromo-methylphthalimides. In one, heating phthalimidoglycyl chloride at 240° effected decarbonylation to the chloromethyl derivative;¹⁹² in the other, N-methylphthalimide with bromine at 160 – 170° gave the



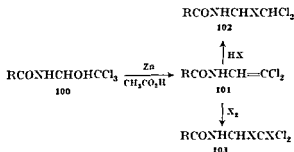
bromomethyl analog reportedly in quantitative yield.¹⁵¹



B. N- α -Haloalkyl-amides and -imides. Because the only α -alkylolamides that have been isolated in pure form are those derived from α -halogenated aldehydes such as chloral and bromal, most known α -haloalkylamides are derived from them. Almost invariably these have been prepared by warming the alkylolamide with phosphorus pentachloride or pentabromide in the absence of solvent.^{106,160,163,204–208}



In order to introduce a structural variation in the product, an indirect procedure has been used.^{208,209} For example, reduction of the alkylolamide **100** with zinc and acetic acid gave the dichlorovinylamide **101**. Either halogen acid (HX) or halogen (X_2) can be added to intermediate **101** to give the α -haloalkylamides **102** and **103**, respectively.



¹⁹² Willard and Hamilton, *J. Am. Chem. Soc.*, **75**, 2370 (1953).

¹⁵¹ Hirve, Gavankar, and Patil, *Proc. Indian Acad. Sci.*, **13A**, 371 (1941) [*C.A.*, **35**, 1593 (1942)].

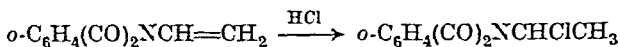
²⁰⁸ Hirve and Rana, *J. Indian Chem. Soc.*, **16**, 677 (1939) [*C.A.*, **34**, 4731 (1940)].

²⁰⁷ Yelburgi, *J. Indian Chem. Soc.*, **10**, 383 (1933) [*C.A.*, **28**, 466 (1934)].

²⁰⁶ Yelburgi and Wheeler, *J. Indian Chem. Soc.*, **11**, 217 (1934) [*C.A.*, **28**, 4377 (1934)].

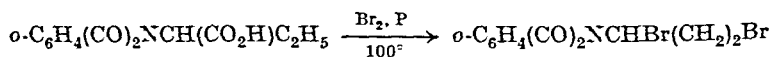
²⁰⁹ Meldrum and Vaid, *J. Indian Chem. Soc.*, **13**, 117 (1936) [*C.A.*, **30**, 4815 (1936)].

Several N- α -haloalkylphthalimides have been obtained in this way from N-vinyl-^{210,211} and N-propenyl-phthalimide.^{212,213} For example, addition of dry hydrogen chloride to the former gave a 97% yield of N- α -chloroethylphthalimide;²¹¹ and addition of bromine gave the corresponding dibromide, $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCHBrCH}_2\text{Br}$.²¹⁰ The latter compound also was

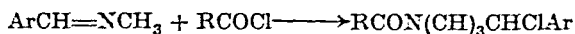


prepared by brominating N-(β -bromoethyl)phthalimide (89% yield) and N-ethylphthalimide (27% yield) with N-bromosuccinimide.²¹⁴

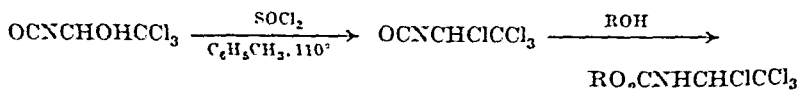
Extension of the decarboxylation reaction mentioned on p. 97 to α -phthalimidobutyric acid produced an α -haloalkyl derivative. When the acid was heated with phosphorus and bromine at 100°, it gave N-(1,3-dibromopropyl)phthalimide in 52% yield.^{212,215}



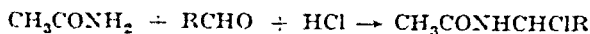
Recent work has shown that acid chlorides will add to imines derived from aromatic aldehydes to give α -chloroalkylamides.²¹⁶



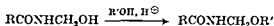
Another recent report describes the preparation of N-(1,2,2,2-tetrachloroethyl)carbamates by the treatment of the corresponding isocyanate with alcohols and phenols.⁷³



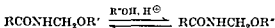
Finally, α -chloroalkyl derivatives of acetamide and of benzenesulfonamide have been prepared in crude form in solution by direct reaction of the amide, an aldehyde, and dry hydrogen chloride.²⁰¹



Ethers of N-Methylol- and N- α -Alkylol-amides. *A. Ethers of N-Methylol-amides and -imides.* These substances are most simply prepared by acid-catalyzed alcoholysis of N-methylolamides. Primary alcohols react more readily than secondary,⁷⁹ and tertiary carbinols do



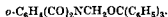
not react at all.²¹⁷ Under similar conditions one ether can be made from another by an alkoxyl interchange process.^{79,218} With mercaptans thioethers are formed.²¹⁹ Excessive amounts of acid are to be avoided



because under such conditions the ethers, like N-methylol compounds, are readily converted to the corresponding methylenebisamides. A pH of about 3 is optimal for stopping the reaction at the ether stage.²¹⁷

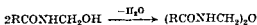
In a few instances N-methoxymethyl derivatives of urea have been obtained by direct condensation of formaldehyde with urea in methanol.^{149,219} The generality of the method, however, has not been established.

Ethers of less reactive alcohols can be prepared by solvolysis of N-halo-methyl-amides or -imides. Thus N-bromomethylphthalimide with triphenylcarbinol gives a 50% yield of the ether.⁷¹

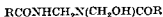


Tertiary carbinols that undergo facile acid-catalyzed elimination, i.e., *t*-butyl alcohol, obviously cannot be etherified in this way.

The tendency for N-methylolamides to undergo self-etherification, i.e.,



varies with the structure of the amide, but etherification usually can be effected in the presence of controlled amounts of mineral acid (see above). The great ease with which ether formation occurred in some reactions, even in alkaline solution, led Einhorn to assign to the ethers the isomeric N-methylol-N,N'-methylenebisamide structure.^{10,153}



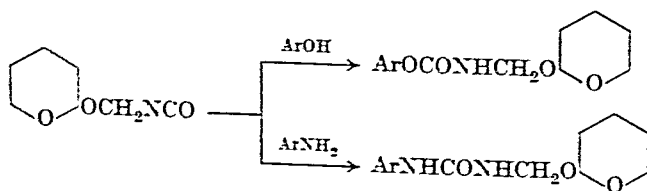
²¹⁷ Bruce and Mantell, *J. Org. Chem.*, **26**, 5176 (1961).

²¹⁸ Zigeuner and Hoselmann, *Monatsh. Chem.*, **88**, 5 (1957).

²¹⁹ Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936) [*C.A.*, **30**, 5944 (1936)]

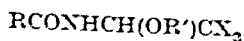
On the basis of chemical evidence, however, Zigeuner preferred the symmetrical ether structure.⁵⁴ Furthermore, the infrared spectra of a series of derivatives of this type prepared from long-chain alkyl amides showed no hydroxyl absorption,²¹⁷ and both the infrared and proton magnetic resonance spectra of the benzamide derivative first reported by Einhorn and co-workers¹⁰ are consistent only for the structure $(C_6H_5CONHCH_2)_2O$.¹⁴ Hence it must be concluded that Einhorn's original structural assignment^{10,153} is in error and should be corrected along with several more recent erroneous assignments.²²⁰⁻²²²

2-Tetrahydropyranyloxymethyl isocyanate has been used recently to prepare ethers of N-methylolcarbamates and of N-methylolureas.⁷³



Once formed, most ethers are stable except to hydrolytic conditions. In hot aqueous solution or in cold 1N alkali they break down to amide, formaldehyde, and alcohol only slightly less rapidly than do the corresponding N-methylol derivatives.⁷³

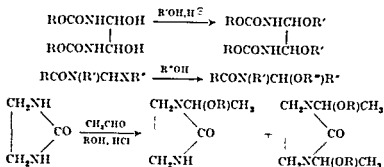
B. Ethers of N- α -Alkylolamides. Because nearly all N- α -alkylolamides are necessarily restricted to derivatives of chloral and bromal (see pp. 93-94), most of the known ethers likewise fall into the general type



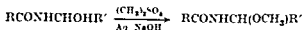
However, among a wide variety of examples the amides used include aliphatic, aromatic, and heterocyclic amides, a lactam, imides, carbamates, and urea derivatives.

Three methods used for the preparation of the N-methylol ethers may also be used for the synthesis of ethers of N- α -alkylolamides. They are acid-catalyzed alcoholysis of the corresponding N- α -alkylol derivative,²²³ alcoholysis of the N- α -haloalkyl compound,^{106,204,206,214} and direct reaction

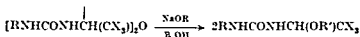
of an amide derivative with an aldehyde in an acidic alcoholic medium.²²⁴



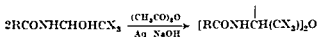
In addition, alkylation with dimethyl sulfate has been employed to prepare a number of methyl ethers.^{101 166 203 225, 226}



A base-catalyzed ether interchange process has been utilized in several instances.¹⁶¹⁻¹⁶³ The symmetrical ether employed as the starting material is readily obtainable from the N-α-alkylol derivative by using



an acid anhydride or an acid chloride under Schotten-Baumann conditions (refs. 94, 95, 160, 161, 163, 166, 168, 207, 208, 226-229). Workers who first encountered this reaction believed that simple elimination had



occurred to produce N-acylimines of type $\text{RCON}=\text{CHCX}_3$.^{94 229 230} It remained for Feist to recognize the bimolecular nature of the dehydration and to assign the correct structure to the symmetrical ethers.⁹⁵ In acid media the dehydration reaction is largely prevented, and normal esterification of the hydroxyl group predominates (see below). In this connection it is known that certain N-acetyl ketimines spontaneously add

²²⁴ Yost, U.S. pat. 2,880,208 [C.A., 54, 569 (1960)]

²²⁵ Hirve and Gavankar, *J. Univ. Bombay*, 6, 11, 123 (1937) [C.A., 32, 3762 (1938)]

²²⁶ Hirve and Rana, *J. Univ. Bombay*, 7, Pt. 3, 174 (1938) [C.A., 33, 3778 (1939)].

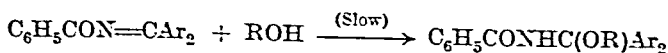
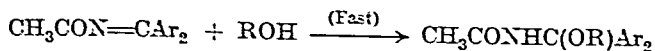
²²⁷ Chattaway, Kerr, and Lawrence, *J. Chem. Soc.*, 1933, 30

²²⁸ Hirve and Patil, *Proc. Indian Acad. Sci.*, 13A, 273 (1941) [C.A., 35, 6250 (1941)].

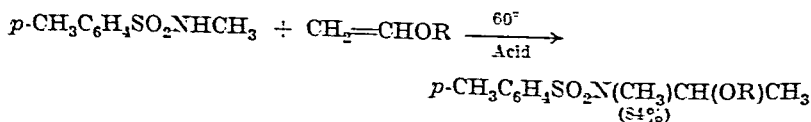
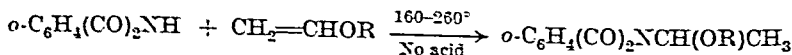
²²⁹ Moscheles, *Ber.*, 24, 1503 (1891).

²³⁰ Hantzsch, *Ber.*, 27, 1243 (1894).

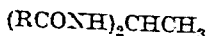
alcohols to give ethers. In contrast, the analogous *N*-benzoyl ketimines do so with comparative reluctance.²³¹



A special method has been applied to the preparation of *N*- α -alkoxyethyl derivatives of imides and of one sulfonamide: reaction with vinyl ethers at elevated temperatures.²³² In the presence of acid, however, the products derived from imides eliminate the elements of alcohol to give

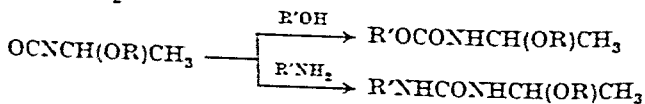
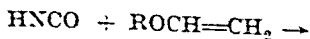


vinyl imides, e.g., $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}=\text{CH}_2$. By contrast, carboxamides and primary sulfonamides generally react with vinyl ethers (with or without acid catalysis) to produce *N,N'*-ethyldenebisamides,

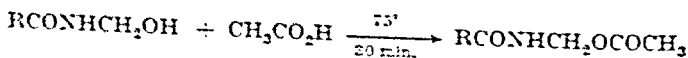


(see below).^{232,233}

Another special method for preparing *N*- α -alkoxyethyl derivatives of carbamyl compounds consists of the treatment of α -alkoxyethylisocyanates with alcohols or amines.²³⁴



Esters of *N*-Methylol- and of *N*- α -Alkylol-amide Derivatives.
A. Esters of N-Methylolamides. *N*-Methylolamides readily undergo acetolysis.⁷⁹ Most esters of *N*-methylolamides, however, have been prepared by conventional acylation methods. These include reaction of



the methylolamide with an acid anhydride alone,^{222,235-237} in the presence of catalytic amounts of sulfuric acid⁵ or of the corresponding sodium salt;²³⁸⁻²⁴¹ treatment with an acid chloride or anhydride in pyridine (refs. 8, 66, 181, 194, 242, 243) or in aqueous alkali;^{237,238,241} and heating with a carboxylic acid in the presence of hydrogen chloride²⁴⁰ or trifluoroacetic anhydride.⁸ The formyl derivative, $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OCHO}$, was prepared (24% yield) by heating N-chloromethylphthalimide in formamide at 100°;²²⁰ N-acetoxymethylmaleimide was obtained (43% yield) by acetolysis of N-chloromethylmaleimide at 100°;⁸ and the phthalimido-methyl esters of a number of carbobenzoxyamino acids and peptides have been prepared by the treatment of N-chloromethylphthalimide with the amino acid in the presence of triethylamine.^{243a}

Esters of N-methylolamides may serve as useful derivatives for isolation and purification. Thus N-methyl-N-methylolacetamide, which could not be obtained in crystalline form, was converted to the acetate $\text{CH}_3\text{CON}(\text{CH}_3)\text{CH}_2\text{OCOCH}_3$, which could be distilled under reduced pressure.²⁴⁴

A direct preparation of esters of N-methylolamides from amides would greatly increase their usefulness as amidomethylating agents. One example of this synthetic simplification is the preparation of N-acetoxymethylstearamide directly from stearamide.¹³⁸ The relatively mild conditions used in the procedure suggest that it may be generally applicable to the synthesis of other esters of this type.

B. Esters of N- α -Alkylolamides. Nearly all substances of this type are either acetates or benzoates of chloral- or bromal-amide derivatives, $\text{RCONHCH}(\text{OCOR}')\text{CX}_2$. They have usually been made by direct acylation of the corresponding hydroxy compound with acetyl chloride or benzoyl chloride either alone^{94,163} or in the presence of pyridine.^{101,166,204} Acetic anhydride with catalytic amounts of concentrated sulfuric acid generally gives the corresponding acetate (refs. 161, 162, 166, 168, 225, 228), but in the presence of aqueous sodium hydroxide it usually produces the symmetrical ether (see p. 101).^{94,95,160} This tendency toward ether formation is also governed, however, by the nature of the α -alkylolamide.

²²² Pikel, U.S. pat. 2,477,346 [C.A., 44, 168 (1950)]

²³⁵ Shipp, U.S. pat. 2,232,483 [C.A., 35, 3459 (1941)]

²³⁷ Spurr, *Roczniki Chem.*, 28, 455 (1954) [C.A., 50, 311 (1956)]

²³⁸ Monti and Venturi, *Gazz. Chim. Ital.*, 78, 365 (1946) [C.A., 42, 1261 (1948)]

²³⁹ Zellner, Austrian pat. 176,561 [C.A., 48, 10778 (1954)]

²⁴⁰ Zellner, Austrian pat. 176,562 [C.A., 48, 10778 (1954)]

²⁴¹ Zellner, Ger. pat. 927,269 [Chem. Zentr., 1955, 7980]

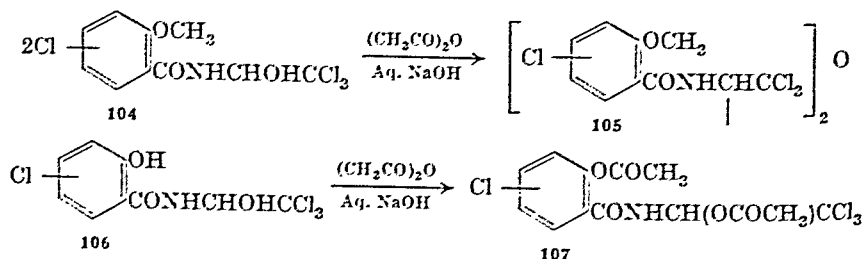
²⁴² Enborn and Friebelmann, *Ann.*, 361, 153 (1958).

²⁴³ Mizuch, Kasatkin, and Gelfer, *J. Gen. Chem. USSR (Engl. Transl.)*, 27, 213 (1957).

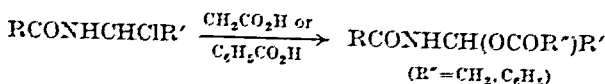
^{243a} Nefkens, *Nature*, 193, 974 (1962). *Rec. Trav. Chim.*, 82, 941 (1963)

²⁴⁴ Walter, Steffen, and Heyns, *Chem. Ber.*, 94, 2462 (1961).

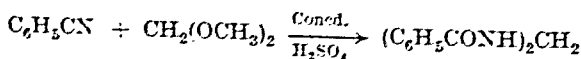
Thus with acetic anhydride and aqueous sodium hydroxide the chloral-amides **104** give mainly the symmetrical ethers **105**. The unmethylated analogs **106**, on the other hand, yield the corresponding acetates **107** as the major products.²²⁶



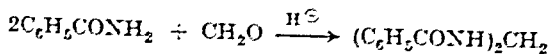
A few esters have been made by acidolysis of the corresponding N- α -chloroalkylamides.^{205,211}



N,N'-Methylenebis-amides and -imides. N,N'-Methylenebisbenzamide was first prepared in 1876 by the action of methylal on benzonitrile in the presence of concentrated sulfuric acid.²⁴⁵ Later this so-called

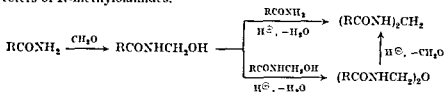


"Hipparaffin" was obtained more readily by heating benzamide with formalin in acid solution.²⁴⁵ Since then this method has become one of general utility, having been applied to many simple amides, some N-

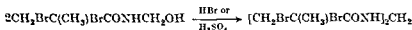


monosubstituted amides,²⁴⁷⁻²⁴⁹ acyclic^{55,153,250,251} and cyclic^{155,252} carbamyl compounds, and a few aromatic sulfonamides.^{55,155} Although mineral acid is most often used as the catalyst, other conditions successfully employed have included heating the components alone or in acetic anhydride or glacial acetic acid, or even warming in the presence of weak

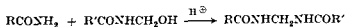
aqueous base (dilute potassium carbonate solution). The ubiquity of this reaction is readily understood from the fact that N,N' -methylenebisamides usually represent the end products (and most stable ones) derived from the reaction of amides with formaldehyde in acid media. Thus N,N' -methylenebisamides are obtainable by acid treatment of both N -methylolamides and symmetrical ethers as well as of unsymmetrical ethers and esters of N -methylolamidés.



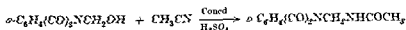
An interesting specificity in catalytic requirement for one of these reactions has been observed recently.²⁵³ Heating N -methylol-2,3-dibromoisobutyramide with aqueous hydrobromic or sulfuric acid gave the corresponding bisamide, but identical treatment with aqueous hydrochloric acid did not. Furthermore, the same transformation could be effected in the presence of bromine but not with iodine.^{253,254}



Perhaps the most general method and the one giving the best yields involves treatment of an amide with an N -methylolamide in acid solution. It has the added advantage of flexibility in that unsymmetrical bisamides are obtainable in this way. These unsymmetrical derivatives can be



prepared also by treatment of nitriles with N -methylolamides in strong sulfuric acid. Thus acetonitrile and N -methylolphthalimide in concentrated sulfuric acid give N -acetylaminomethylphthalimide in 93% yield.⁸⁴

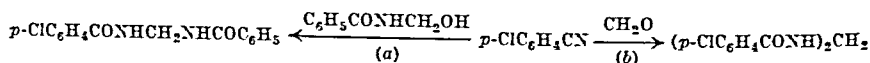


Under these conditions nitriles react more readily with N -methylolamides than they do with formaldehyde. A study designed to test this generalization showed that in a formic-sulfuric acid solution at 30° a mixture of

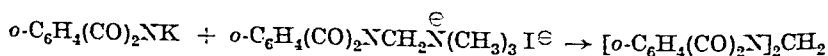
²⁵³ Feuer and Bello, *J. Am. Chem. Soc.*, **78**, 4367 (1956).

²⁵⁴ Feuer and Lynch, *J. Am. Chem. Soc.*, **75**, 5027 (1953).

p-chlorobenzonitrile, formaldehyde, and *N*-methylolbenzamide gave almost exclusively the unsymmetrical bisamide (reaction *a*).²⁵⁵

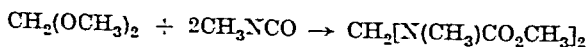


A few special methods have been employed for making certain methylenebis-amides and -imides. *N,N'*-Methylenebisphthalimide has been prepared by treating potassium phthalimide with methylene iodide²⁵⁶ or, preferably (48% yield), with the methiodide of *N*-dimethylaminomethylphthalimide.⁸¹ Similarly, chloromethylamides^{178,194} and aminomethylamides^{82,257} have been used to amidomethylate imides and sulfonamides

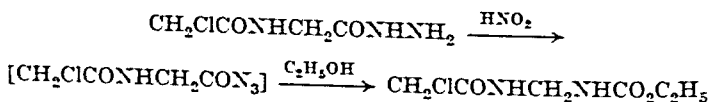


or their alkali metal salts.

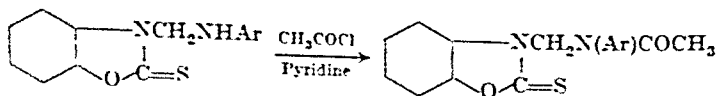
A recently reported method for preparing *N,N'*-methylenebisurethans appears to be general.²⁵⁸ An example is the reaction of methylal with two equivalents of methyl isocyanate to give dimethyl *N,N'*-dimethyl-*N,N'*-methylenebiscarbamate. Thioformals react analogously to give



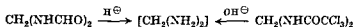
methylenebisthiocarbamates. By another apparently general process, unsymmetrical combinations of amides with urethan have been obtained through the Curtius reaction of *N*-acylglycylhydrazides.^{157,259}



Finally, acetylation of the Mannich-type products derived from some anilines and an oxazolidinethione has given several unsymmetrical bisamides.²⁶⁰

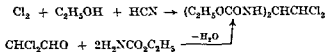


N,N'-Methylenebisamides generally are stable crystalline solids. N,N'-Methylenebisbenzamide can be sublimed,²⁴⁵ and N,N'-methylenebisphenylacetamide can be distilled.²⁶¹ Compounds of this type usually are stable in 1N sodium hydroxide at 90°, ⁷⁹ but treatment with hot dilute mineral acid reconverts them to the corresponding amides. As expected, hot concentrated acid or hot alcoholic alkali hydrolyzes them to the carboxylic acids.^{245,261} Of some interest is the report that methylenediamine can be prepared in solution by hydrolysis of N,N'-methylenebisformamide with cold concentrated mineral acid.²⁶² Einhorn had previously reported similar results from the alkaline hydrolysis of N,N'-methylenebistrichloroacetamide.^{263,264}



Treatment of methylenebisurea with dilute hydrochloric acid leads to polymeric products of the type $\text{H}_2\text{NCONH}(\text{CH}_2\text{NHCONH})_n\text{H}$.^{219,265}

N,N'-Alkylidene- and -Arylidene-bisamides. The first example of this type, diethyl N,N'-dichloroethylidenebiscarbamate, was prepared in 1840 by the action of chlorine on an ethanolic solution of hydrocyanic acid.²⁶⁶ Its structure, however, was not determined until thirty years



later, when it was obtained by the reaction of dichloroacetaldehyde with urethan.^{173,267} The latter method has been the basis for the preparation of several hundred compounds of this class. Synthetic variations include heating the components together without solvent,²⁶⁸⁻²⁷⁰ in ethanol,^{271,272}

²⁶¹ Hepp, *Ber.*, **10**, 1649 (1877).

²⁶² Knudsen, *Ber.*, **47**, 2698 (1914).

²⁶³ Einhorn, *Ann.*, **343**, 207 (1903).

²⁶⁴ Einhorn and Newermayer, *Ann.*, **343**, 305 (1903).

²⁶⁵ Staudinger and Wagner, *Makromol. Chem.*, **12**, 168 (1954) [*C.A.*, **49**, 12302 (1955)].

²⁶⁶ Stenhouse, *Ann.*, **33**, 92 (1840).

²⁶⁷ Bischoff, *Ber.*, **5**, 80 (1872).

²⁶⁸ Bojanović, Vondjel, Mihailović, and Stefanović, *Ber. Chem. Ges. Belgrade*, **20**, 267 (1955) [*Chem. Zentr.*, 1957, 6712].

²⁶⁹ Ittyerah and Pandya, *Proc. Indian Acad. Sci.*, **15A**, 258 (1942) [*C.A.*, **37**, 2725 (1943)].

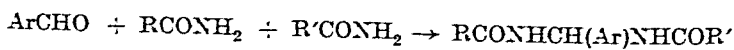
²⁷⁰ Schiff, *Ann.*, **148**, 330 (1868).

²⁷¹ Nigam and Pandya, *Proc. Indian Acad. Sci.*, **29A**, 56 (1949) [*C.A.*, **43**, 6182 (1949)].

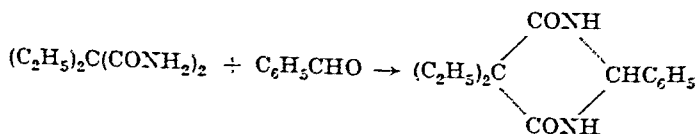
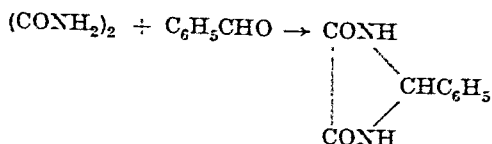
²⁷² Schiff, *Ann.*, **151**, 186 (1869).

water,^{123,272} pyridine,²⁷³⁻²⁷⁶ aqueous acid,^{173,277,278} glacial acetic acid,^{154,279} or acetic anhydride.²⁵⁰⁻²⁵² The last method appears to be the most generally useful. However, condensation in refluxing benzene with azeotropic removal of water has also met with moderate success.²⁸³

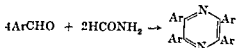
Most of the commonly available primary amides and carbamyl compounds have been utilized in reactions with aldehydes. Even a few *N*-monosubstituted amides have been included.^{270,276} By heating benzaldehyde and 2-furaldehyde with mixtures of two different amides, mixed *N,N'*-benzylidene- and *N,N'*-furylidene-bisamides have been obtained in yields ranging from 25 to 42%.²⁸⁴



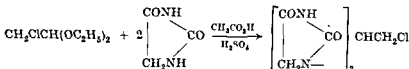
Diamides with suitably positioned functional groups yield cyclic bisamides. Oxamide and malonamide derivatives lead to diketotetrahydroimidazoles²³⁵ and diketohexahydropyrimidines,²⁸⁶ respectively.



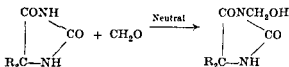
aldehydes. One reason is the occurrence of a side reaction in which tetra-substituted pyrazines are formed.^{271,287}



Phthalimide does not react with benzaldehyde even in the presence of acetic anhydride.⁸⁵ This behavior is consistent with the fact that hydantoins undergo *acid-catalyzed* condensation with acetals (and with formaldehyde^{185,232,288,289}) preferentially at the amide nitrogen atom.²⁹⁰

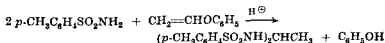


In interesting contrast is the demonstration that in *neutral* solution formaldehyde reacts at the imide nitrogen atom to give the 3-methylol derivative.¹⁸⁷ This alteration in reaction course is consistent with the



idea that the acid-catalyzed process involves attack at the more nucleophilic (amide) nitrogen atom by a protonated aldehyde species,²⁹⁰ while the reaction in neutral solution occurs through attack of the neutral aldehyde by the anion derived from the more acidic (imide) nitrogen atom

Sulfonamides, likewise, do not react readily with aldehydes to give bisamides. Ethylidenebis-(*p*-toluenesulfonamide), however, has been obtained (11% yield) from the acid-catalyzed reaction of *p*-toluenesulfonamide with phenyl vinyl ether.²³² This appears to be a general method for preparing the corresponding biscoxamides as well.^{232,233}



Simple ketones, unlike aldehydes, do not react with amides. Perfluorinated ketones, however, might be expected to behave like aldehydes and

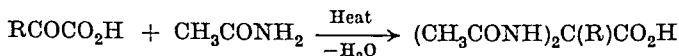
²⁸⁷ Bülow, *Ber.*, **26**, 1972 (1893).

²⁸⁸ Rogers, U.S. pat. 2,404,096 [*C.A.*, **40**, 6096 (1946)]

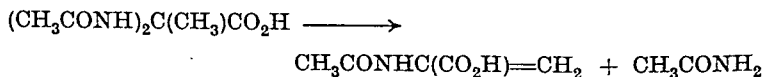
²⁸⁹ Walker, U.S. pat. 2,417,999 [*C.A.*, **41**, 4511 (1947)]

²⁹⁰ Johnson and Crosby, *J. Org. Chem.*, **27**, 2077 (1962).

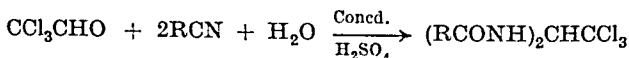
give bisamides, provided that the reaction does not stop at the α -alkylol stage, as it usually does with perhalogenated aldehydes, i.e., chloral. This supposition gains support from the fact that both pyruvic acid²⁹¹ and benzoylformic acid²⁹² give bisamides with acetamide. The pyruvic acid



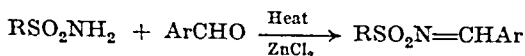
derivative loses one acetamide residue in hot glacial acetic acid, and α -acetamidoacrylic acid is formed.²⁹²⁻²⁹⁴



If proper conditions are employed, even chloral and its analogs yield bisamides rather than the usual α -alkylol compounds. The conditions include the use of concentrated sulfuric acid as the condensing agent either with a nitrile^{4,245,261,295} or with an amide.²⁹⁶ However, a possible side



reaction in this and similar condensations of aromatic aldehydes with carboxamides and sulfonamides must be anticipated. When a Lewis acid is used as a catalyst in the condensation of a sulfonamide with an aromatic aldehyde, an arylidenemonoamide (or sulfonylimine) is produced.¹⁵⁹



Of some interest is the observation that the three hydroxybenzaldehydes react with amides to give the acylimines, $\text{ArCH}=\text{NCOR}$, under the same conditions that lead to bisamides, $\text{ArCH}(\text{NHCOR})_2$, from the corresponding methoxybenzaldehydes.^{296a,297-299} Similarly, 5-chloro- and 3,5-dichlorosalicylaldehyde, when heated with heptanamide, benzamide, or benzene-sulfonamide, give only the acylimine (or sulfonylimine) derivatives even though no Lewis acid is present.²⁷¹ However, these are exceptional cases.

²⁹¹ Bergmann and Grafe, *Z. Physiol. Chem.*, **187**, 187 (1930).

²⁹² Shemin and Herbst, *J. Am. Chem. Soc.*, **60**, 1954 (1938).

²⁹³ Sals, *Ann.*, **569**, 153 (1950).

²⁹⁴ Wieland, Ohnacker, and Ziegler, *Chem. Ber.*, **90**, 194 (1957).

²⁹⁵ Hubner, *Ber.*, **6**, 109 (1873).

²⁹⁶ Batt and Woodcock, *J. Chem. Soc.*, **1948**, 2322.

^{296a} Mehra and Pandya, *Proc. Indian Acad. Sci.*, **10A**, 285 (1939) [*C.A.*, **34**, 1981 (1940)].

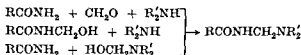
²⁹⁷ Manzur and Pandya, *Proc. Indian Acad. Sci.*, **10A**, 282 (1939) [*C.A.*, **34**, 1980 (1940)].

²⁹⁸ Mehra and Pandya, *Proc. Indian Acad. Sci.*, **10A**, 279 (1939) [*C.A.*, **34**, 1980 (1940)].

²⁹⁹ Pandya and Sodhi, *Proc. Indian Acad. Sci.*, **7A**, 361 (1938) [*C.A.*, **32**, 7434 (1938)].

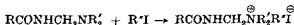
As a rule, alkylidene- and arylidene-bisamides resemble the methylenebisamides in their high thermal stability and in their behavior toward acids and bases.

N-Aminomethylamides and Their Quaternary Salts. The voluminous literature dealing with N-aminomethylamides has been reviewed recently.³ No purpose would be served by repeating this information here. It should suffice to note that three related methods have been used to synthesize these compounds: a Mannich-type reaction of amides with formaldehyde and amines,^{79,257,300-302} reaction of amines with N-methylolamides,^{79,68,303} and reaction of amides with N-methylolamines or N,N'-methylenediamines.³⁰³ The first method is, by far, the

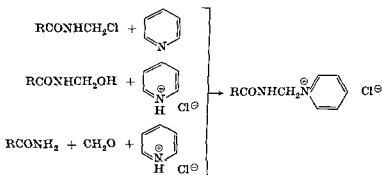


most convenient and, consequently, the most commonly used.

Three types of quaternary salts of N-aminomethylamides are known. The first is prepared by alkylation of the tertiary amine with methyl or ethyl iodide.^{1,179,180,194,304} The second is obtained by treating pyridine



with an N-chloromethylamide (pure⁶⁶ or prepared *in situ*^{199,200,305}), or by reaction of pyridine hydrochloride in pyridine either with a preformed N-methylolamide^{140,235,243} or with an amide and formaldehyde.^{138,306}



³⁰⁰ Bohme, Dietz, and Leidreiter, *Arch. Pharm.*, **287**, 198 (1934).

³⁰¹ Einhorn, Ger. pat. 284,440 [*Chem. Zentr.*, **1915**, II, 108].

³⁰² Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

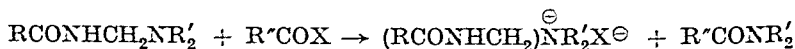
³⁰³ Weaver, Simons, and Baldwin, *J. Am. Chem. Soc.*, **66**, 222 (1944).

³⁰⁴ Hellmann and Loschmann, *Chem. Ber.*, **87**, 1684 (1954).

³⁰⁵ Hunt and Bradley, U.S. pat. 2,493,088 [*C. A.*, **44**, 3041 (1950)].

³⁰⁶ Baldwin, Evans, and Salkeld, U.S. pat. 2,278,417 [*C. A.*, **36**, 5032 (1942)].

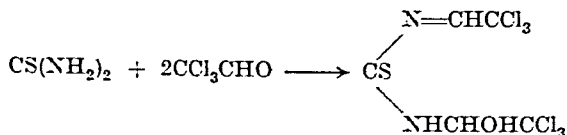
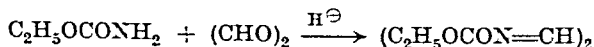
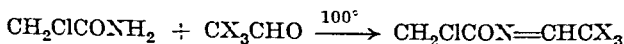
The third results when an aminomethylamide is heated with an acid halide.¹⁹¹



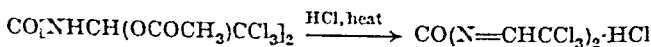
N-Acyl- and N-Sulfonyl-imines. Consideration of compounds of this type will be restricted to derivatives of aldehydes and ketones lacking an α -hydrogen atom. When an α -hydrogen atom is present, tautomerization to the corresponding enamide becomes possible (see pp. 115–116).

As stated previously, reactions of amides with aromatic aldehydes generally lead to N,N'-arylidenebisamides. A number of hydroxybenzaldehyde derivatives are exceptions to this rule and give acylimines instead.^{271,297–299} These have been noted on p. 110.

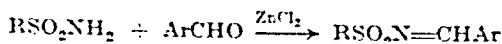
Several other amide-aldehyde combinations also react anomalously. These are chloroacetamide with chloral and bromal,³⁰⁷ urethan with glyoxal,³⁰⁸ and thiourea with chloral.¹⁶⁰ For the last combination, reaction occurs normally at one nitrogen atom to give the chloralurea derivative, but abnormally at the other to give the acylimine structure.



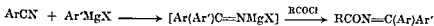
Bis-trichloroethylideneurea has been prepared by the elimination of 2 moles of acetic acid from the diacetate of chloralurea.¹⁶⁰



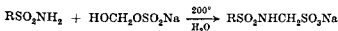
Although sulfonamides react with chloral to give the corresponding N- α -alkylolamides, they condense with aromatic aldehydes to the N-sulfonylimines.¹⁵⁹ Zinc chloride is used as a catalyst. Interestingly, sulfonylimines are also obtained from the reaction of 2-furamide with arenesulfonyl chlorides in pyridine solution.¹⁵⁹



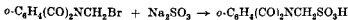
N-Acyl derivatives of aromatic ketimines can be prepared by acylation of the isolated imine.²³¹ It is usually more convenient, however, to acylate the intermediate halomagnesium derivative obtained by the action of an aromatic Grignard reagent on an aromatic nitrile.^{19,120,231}



Amidomethanesulfonic Acids and Their Sodium Salts. Few compounds of this type have been reported since Knoevenagel and Lebach first made them in 1904 by heating carboxamides or sulfonamides with aqueous sodium formaldehyde bisulfite under pressure.¹³² The only



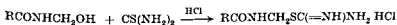
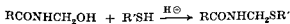
sulfonic acid of this class was prepared by the reaction of N-bromomethylphthalimide with aqueous sodium sulfite.³⁰⁹



Related Compounds of Potential Utility as Electrophilic Reagents

Many compounds not yet employed as α -amidoalkylating agents bear a sufficient structural resemblance to those that have been so employed to suggest that the former might react analogously to the latter under suitable conditions. In the compilation that follows, an attempt has been made, mainly on the basis of structural analogy, to place the more likely candidates ahead of the less likely ones. For this reason the cyclic analogs, which might be expected to be most stable and least reactive, have been placed last.

Amidomethyl Thio Ethers and Thiol Esters. *A. From N-Methylolamides and Mercaptans*^{79,219,310,311} or *Thiourea*.^{312,313}



³⁰⁹ Balaban, *J. Chem. Soc.*, 1928, 569

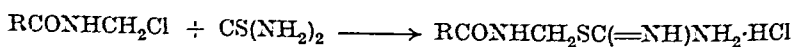
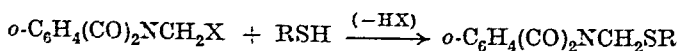
³¹⁰ Benson and Cairns, *J. Am. Chem. Soc.*, 70, 2115 (1948).

³¹¹ Monti and Franchi, *Gazz. Chim. Ital.*, 85, 510 (1955) [*C. A.*, 50, 4952 (1956)]

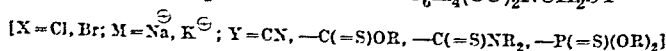
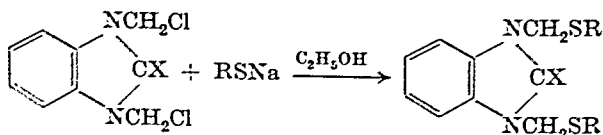
³¹² Albrecht, Frei, and Sallmann, *Helv. Chim. Acta*, 24, 233E (1941)

³¹³ Société pour l'Industrie Chimique à Bâle, Fr. pat. 849,147 [*C. A.*, 35, 6357 (1941)].

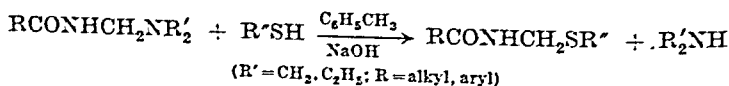
B. From *N*-Halomethyl-amides^{190,195,314} or -imides^{190,315} and Mercaptans^{190,315} or Thiourea.^{195,314}



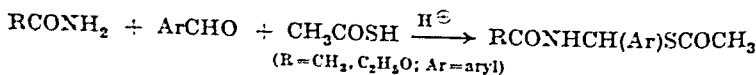
C. From *N*-Halomethyl-amides¹⁹⁸ or -imides^{8,104,316,317} or Carbamyl Compounds^{178-180,318} and Alkali Metal Mercaptides,¹⁷⁸⁻¹⁸⁰ Thiocyanates,^{8,104,193} Xanthates,³¹⁷ Dithiocarbamates,³¹⁷ or Dithiophosphates.³¹⁶



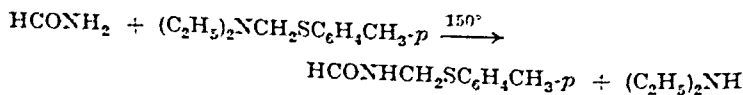
D. From Dialkylaminomethylamides and Mercaptans.³¹⁹



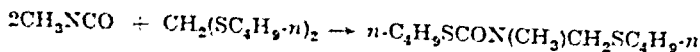
E. From Amides, Aldehydes, and Thiolacetic Acid.³²⁰

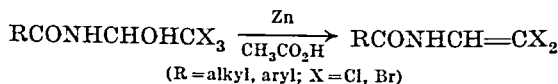
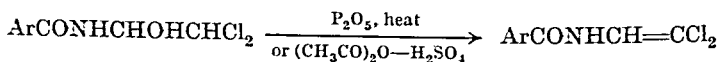
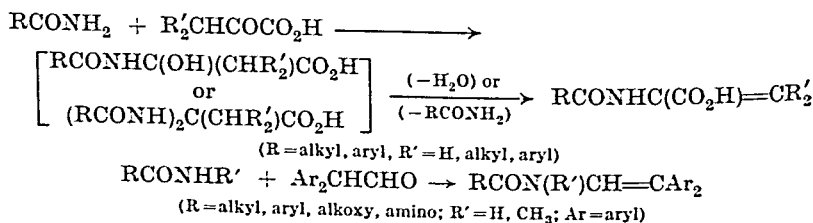
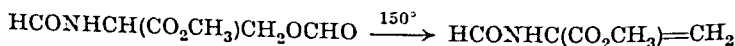
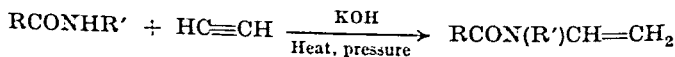
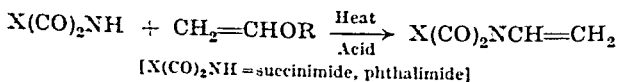
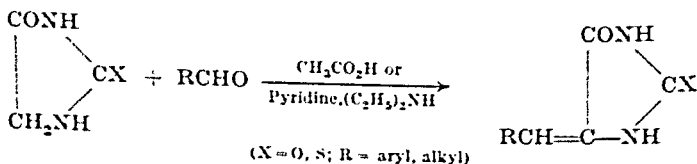


F. From Formamide and an Aminomethyl Sulfide.²²⁹

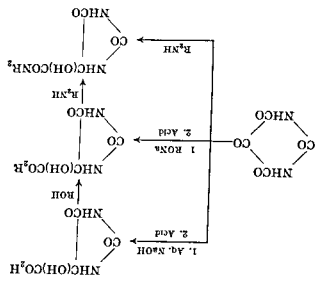


G. From Methyl Isocyanate and Thioformals.²⁵³

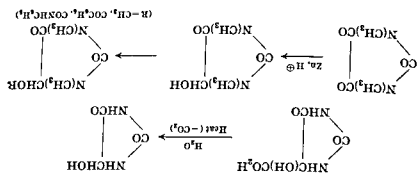


A. By Reduction of Chloral- or Bromal-amides.²⁰⁷⁻²⁰⁹B. By Dehydration of Dihaloacetalamides.²⁰⁸C. From Amides and α -Keto Acids²⁹¹⁻²⁹⁴ or Diarylacetaldehydes.^{324a}D. From the Methyl Ester of *N,O*-Diformyl-DL-serine.³²⁵E. By Vinylation of Amides.³²⁶F. By Vinylation of Imides.²³²G. From Hydantoins and Aldehydes.³²⁷^{207a} Eiden and Nagar, *Arch. Pharm.*, **296**, 445 (1963).²⁰⁸ Heyns and Heinecke, *Z. Physiol. Chem.*, **331**, 45 (1963).²⁰⁹ Reppe, *Neue Entwicklungen auf dem Gebiet der Chemie des Acetylens und Kohlenoxyds*, Springer-Verlag, 1949, pp. 20-21; Copenhaver and Bigelow, *Acetylene and Carbon Monoxide Chemistry*, Reinhold, 1949, pp. 66-67.²³² Ware, *Chem. Rev.*, **48**, 431-433 (1950).

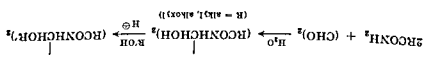
5-Hydroxyhydantoin. *d. Alloxanic Acid Derivatives from* ^{9,328} *Alloxan.*



B. 5-Hydroxyhydantoin from Alloxanic Acid and 1,3-Dimethylparabanic Acid. ³²⁹

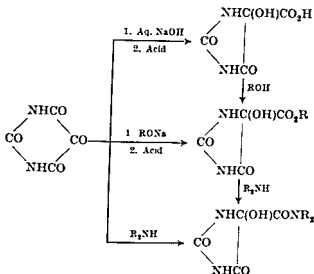


A. From Glyoxal and Amides or Carbamates, 223,330
 Glycol Amides, Carbamates, and Ureas, and Derived Products.

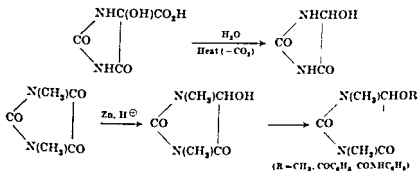


³²⁹ Fisher and Day, *J. Am. Chem. Soc.*, **77**, 4894 (1955).
³²⁸ Biltz and Kobel, *Ber.*, **54**, 1802 (1921). Biltz and Heidrich, *ibid.*, **54**, 1829 (1921).
³²⁷ Badische Anilin and Soda Fabrik A.-G., Fr. pat. 1,128,263 (*Chem. Zentr.*, 1959, 1605).

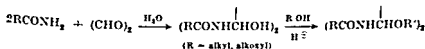
5-Hydroxyhydantoin. *A. Alloxanic Acid Derivatives from Alloxan.*^{9,328}



*B. 5-Hydroxyhydantoin from Alloxanic Acid and 1,3-Dimethylparabanic Acid.*³²⁹



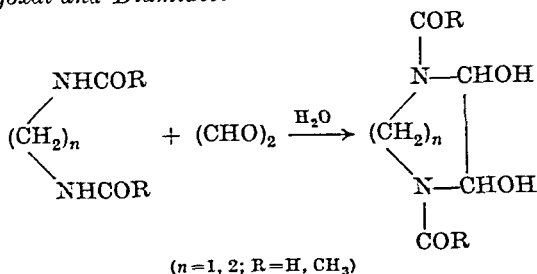
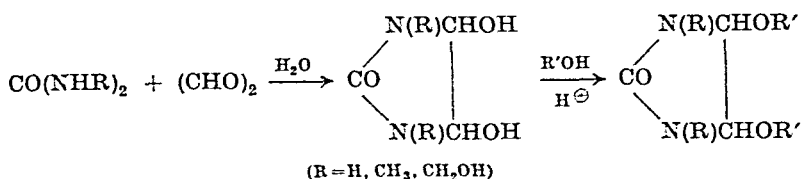
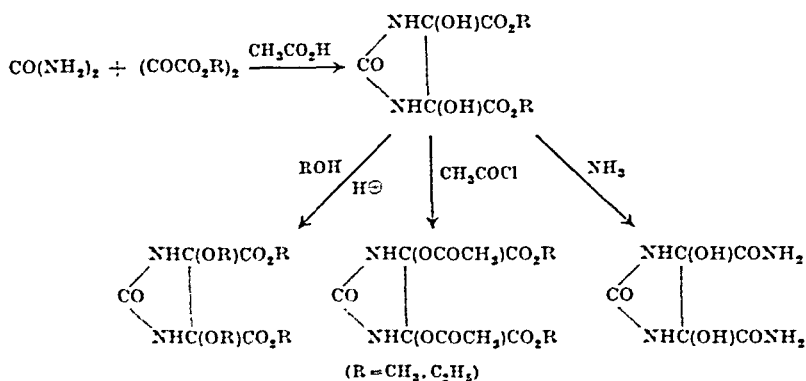
Glycol Amides, Carbamates, and Ureas, and Derived Products.
A. From Glyoxal and Amides or Carbamates^{330 330}



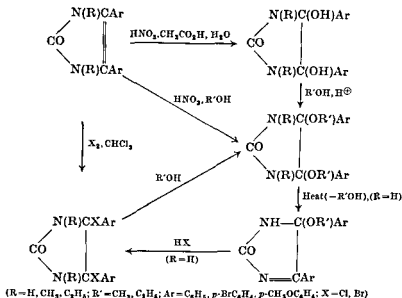
³²⁸ Fisher and Day, *J. Am. Chem. Soc.*, **77**, 4994 (1955).

³²⁹ Hiltz and Kolbel, *Ber.*, **54**, 1802 (1921). Hiltz and Hendrich, *ibid.*, **54**, 1929 (1921).

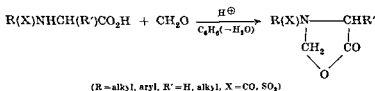
³³⁰ Badische Anilin and Soda-Fabrik A.-G., Fr. pat. 1,129,263 (*Chem. Zentr.*, 1933, 1603).

B. From Glyoxal and Diamides.³³¹C. From Glyoxal and Ureas.^{223,308,332-335}D. From Diketosuccinic Esters and Urea.³³⁶³³¹ Vail, Moran, Moore, and Kullman, *J. Org. Chem.*, **27**, 2071 (1962).³³² Badische Anilin and Soda-Fabrik A.-G., Brit. pat. 720,386 [*C.A.*, **49**, 9326 (1955)].³³³ Reibnitz, U.S. pat. 2,731,472 [*C.A.*, **50**, 13999 (1956)].³³⁴ Slezak, Bluestone, Magee, and Wotiz, *J. Org. Chem.*, **27**, 2181 (1962).³³⁵ Vail, Murphy, Frick, and Reid, *Am. Dyestuff Repts.*, **50**, 27 (1961) [*C.A.*, **55**, 19254 (1961)].³³⁶ Geisenheimer and Anschütz, *Ann.*, **306**, 38 (1899).

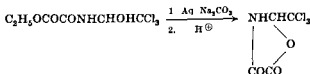
E. From 4,5-Diaryl-2-imidazolones. 337-343



Cyclic Esters and Carbamates of N-α-Alkylolamides. A. N-Acyl- and N-arenesulfonyl-5-oxazolidinones. 344-347



B. 2-Trichloromethyl-4,5-oxazolidinedione 160



337 Biltz, *Ber.*, **41**, 167, 1754, 1761 (1908)

338 Biltz, *Ann.*, **368**, 262 (1909).

339 Biltz and Behrens, *Ber.*, **43**, 1990 (1910).

340 Biltz and Kosegarten, *Ann.*, **368**, 219, 228, 236 (1909).

341 Biltz and Krebs, *Ann.*, **368**, 218 (1909).

342 Biltz and Rumpel, *Ann.*, **368**, 173, 201, 206 (1909)

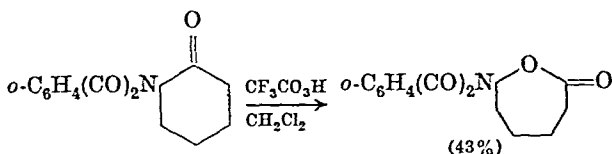
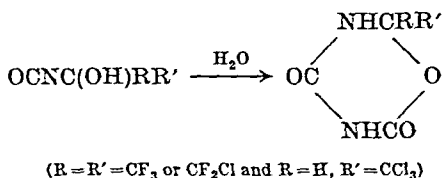
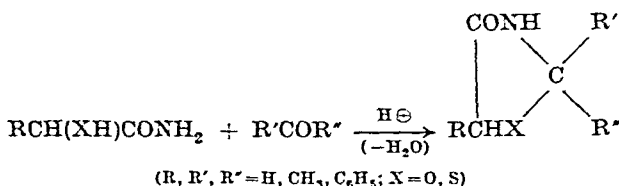
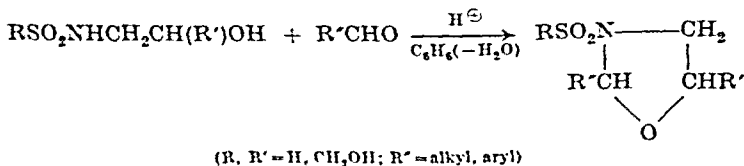
343 Dunnivant, *J. Org. Chem.*, **21**, 1513 (1956).

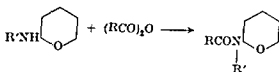
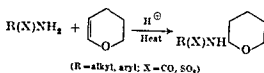
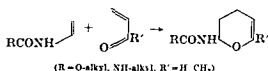
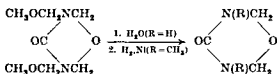
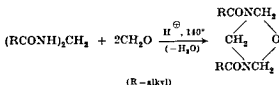
344 Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 5736 (1957).

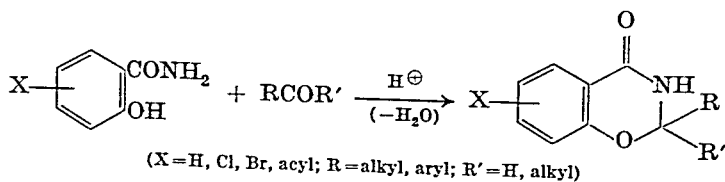
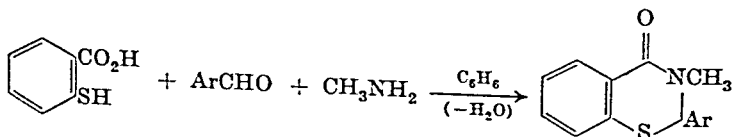
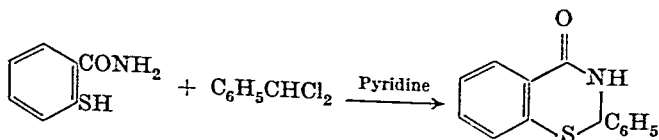
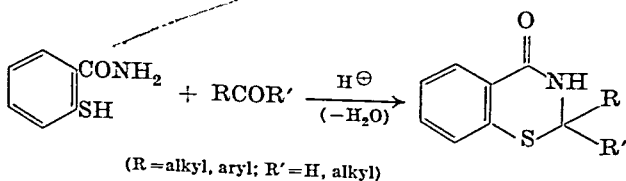
345 Chemische Fabrik auf Aktien, Ger. pat. 148,669 (*Chem. Zentr.*, 1904, I, 411).

346 Chemische Fabrik auf Aktien, Ger. pat. 153,860 (*Chem. Zentr.*, 1904, II, 678).

347 Micheel and Thomas, *Chem. Ber.*, **90**, 2906 (1957).

C. ϵ -Phthalimido- ϵ -caprolactone.³⁴⁸D. 1,3,5-Oxadiazine-2,4-diones.⁷³Cyclic Ethers and Thio Ethers of N- α -Alkylolamides. A. 4-Oxazolidinones and 4-Thiazolidinones.³⁴⁹⁻³⁵¹B. N-Sulfonyloxazolidines.³⁵²³⁴⁸ Smiesman and Bergen, *J. Org. Chem.*, **27**, 2316 (1962).³⁴⁹ Davies, Ramsey, and Stove, *J. Chem. Soc.*, 1949, 2633.³⁵⁰ Fischer, Dangschat, and Stettiner, *Ber.*, **65**, 1032 (1932).³⁵¹ Michael and Jeanprêtre, *Ber.*, **25**, 1678 (1892).³⁵² Rätz, U.S. pat. 2,722,531 [*C.A.*, **50**, 3503 (1956)].

C. *N*-(2-Tetrahydropyranyl)amides.³⁵³⁻³⁵⁵D. *N*-[2,3-Dihydropyranyl-(2)]-carbamates and -carbamides.³⁵⁶E. *Urons*.³⁵⁷F. *Diacyltetrahydro-1,3,5-oxadiazines* ³⁰⁵³⁵³ Glacet and Troude, *Compt. rend.*, **253**, 681 (1961).³⁵⁴ Glacet and Overbøke, *Compt. Rend.*, **255**, 316 (1962).³⁵⁵ Speciale, Ratta, and Marco, *J. Org. Chem.*, **26**, 4311 (1961).³⁵⁶ Schulz and Hartmann, *Chem. Ber.*, **95**, 2735 (1962).³⁵⁷ Brachem, Oppelt, Cowen, Schuckedantz, and Maier, *J. Org. Chem.*, **28**, 1876 (1963).

G. 2,3-Dihydro-1,3-benzoxazin-4-ones.^{166,278,350,358-374}H. 2,3-Dihydro-1,3-benzthiazin-4-ones.^{358,375-377}

- ³⁵⁸ Böhme and Boeing, *Arch. Pharm.*, **294**, 556 (1961).
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³⁶⁰ Hirwe and Rana, *J. Univ. Bombay*, **8**, Pt. 3, 243 (1939) [*C.A.*, **34**, 2819 (1940)].
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³⁶² Hughes and Titherley, *J. Chem. Soc.*, **99**, 23 (1911).
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³⁶⁴ Kaufmann, *Arch. Pharm.*, **285**, 226 (1927) (*Chem. Zentr.*, 1927, II, 88).
³⁶⁵ Keane and Nicholls, *J. Chem. Soc.*, **91**, 264 (1907).
³⁶⁶ Moucka and Rögl, *Ber.*, **59**, 756 (1926).
³⁶⁷ Mowry, Yanko, and Ringwald, *J. Am. Chem. Soc.*, **69**, 2358 (1947).
³⁶⁸ Ohnacker, Brit. pat. 806,729 [*C.A.*, **53**, 14127 (1959)] (same as Ger. pat. 1,028,999).
³⁶⁹ Ohnacker, Ger. pat. 1,021,848 [*C.A.*, **54**, 4633 (1960)].
³⁷⁰ Ohnacker and Scheffler, Ger. pat. 1,063,169 [*C.A.*, **55**, 12432 (1961)].
³⁷¹ Ohnacker and Scheffler, U.S. pat. 2,943,087 [*C.A.*, **54**, 24818 (1960)].
³⁷² Rana, *J. Indian Chem. Soc.*, **19**, 299 (1942) [*C.A.*, **37**, 2361 (1943)].
³⁷³ Titherley, *J. Chem. Soc.*, **91**, 1419 (1907).
³⁷⁴ Titherley and Hicks, *J. Chem. Soc.*, **95**, 908 (1909); Titherley and Hughes, *ibid.*, **97**, 1368 (1910).
³⁷⁵ Böhme and Schmidt, *Arch. Pharm.*, **286**, 330 (1953).
³⁷⁶ Boudet, *Bull. Soc. Chim. France*, **1955**, 1518.
³⁷⁷ Loew, *J. Org. Chem.*, **28**, 2160 (1963).

CHOICE OF EXPERIMENTAL CONDITIONS

It is difficult to make generalizations about optimum conditions for carrying out the numerous reactions included in this review. Impressions in this regard are best derived from the specific discussions of the foregoing section. A few general remarks can be made at this point, however.

Choice of Reactants

If the end product sought from an amidoalkylation reaction is the amine, an amidoalkylation reagent with an easily removable acyl group is to be preferred. This is especially important when the reaction product may not resist treatment with the strong acid or base often necessary for acyl cleavage. Thus the phthalimido group of *p*-phthalimidomethylphenol could not be removed, either by the hydrazine method or by hydrolytic means¹⁵ without destroying the molecule. Similarly no way was found to hydrolyze derivatives of the type $\text{ArCH}(\text{C}_6\text{H}_5)\text{NHCOR}$ (Ar = hydroxyaryl; R = CH_3 or C_2H_5) to the corresponding amines.⁷⁴ Consistent with these results is the observation that the ease of acid hydrolysis of amides of the type $\text{ArCH}_2\text{NHCOR}$ (Ar = hydroxyaryl) decreased in the order $\text{R} = \text{H}$, C_2H_5 , CH_3 , C_6H_5 , and that the formamide derivative was especially easily hydrolyzed.⁷⁵

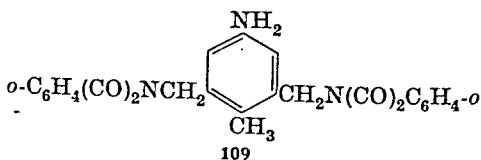
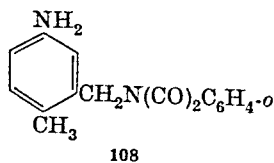
To obtain the best yield of monosubstitution product from a relatively reactive substrate it is often desirable to select an amidoalkylating agent of minimal reactivity. Excessive reactivity generally leads to polysubstitution and consequent reduction in yield of the desired product.

When attempts were made to amidomethylate relatively unreactive substrates with *N*-methylolamides under acid-catalyzed conditions, methylenebisamides, $(\text{RCONH})_2\text{CH}_2$, were often encountered as by-products,^{20,47} and sometimes as the only products. (*N*-Methylolbenzamide is especially prone to disproportionate in this way.) This result is an indication that the use of a more electrophilic reagent, e.g., *N*-methylolphthalimide, may be in order or that more strongly acidic conditions might be employed to force the reaction in the desired direction.

Choice of Conditions

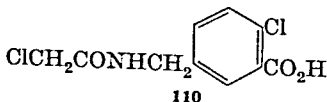
In most reactions, monosubstitution is favored by increasing the ratio of substrate to reagent. In a few favorable instances either mono- or di-substitution can be effected at will, each to the virtual exclusion of the other, merely by using the reactants in the proper stoichiometric ratio. Thus equivalent quantities of *p*-toluidine and *N*-methylolphthalimide in

concentrated sulfuric acid gave the monosubstitution product **108** in 81 % yield,⁴⁴ whereas two equivalents of the phthalimide reagent gave the



disubstituted derivative **109** in 95 % yield under the same conditions.²⁹

Even the concentrations of reactants can be varied to affect the yield. For example, in the reaction of *o*-chlorobenzoic acid with *N*-methylolchloroacetamide to give the product **110**, the 65 % yield obtained was reduced to 40 % when the quantity of sulfuric acid was halved.⁵⁷ The



generality of this effect of concentration on yield has not been established, but it should be regarded as a potentially important variable.

EXPERIMENTAL PROCEDURES

α -Amidoalkylation of Aromatic Carbon Atoms

***N*-(2-Hydroxy-3,5-dinitrobenzyl)phthalimide from 2,4-Dinitrophenol and *N*-Methylolphthalimide in 5% Oleum.**⁶⁹ An intimate mixture of 9 g. (0.049 mole) of 2,4-dinitrophenol and 9 g. (0.051 mole) of *N*-methylolphthalimide is gradually added to 35 g. of 5 % fuming sulfuric acid cooled in ice. After the mixture has stood at room temperature for 10 minutes with occasional stirring, it is warmed slowly and finally heated for 40 minutes on the steam bath. The cooled reaction mixture is then poured in a thin stream into 200 ml. of vigorously stirred ethanol, and the resulting mixture is boiled for 1–2 minutes. After it has cooled, the precipitate is collected and recrystallized from nitrobenzene or glacial acetic acid to give 16.8 g. (95 %) of the *N*-arylmethylphthalimide, m.p. 210–211°.

2-Chloro-5-(chloroacetylaminomethyl)benzoic Acid from 2-Chlorobenzoic Acid and *N*-Methylolchloroacetamide in Concentrated Sulfuric Acid.⁵⁷ A mixture of 277.8 g. (1.76 moles) of 2-chlorobenzoic acid and 700 ml. of concentrated sulfuric acid is stirred

and cooled to 20°. Powdered N-methylolchloroacetamide (202 g., 1.8 moles) is added over a 30-minute period while the temperature is maintained at 20°. The reaction mixture is stirred overnight, and the solution is poured over ice and allowed to stand for 2 days. The solid is collected, washed with water, dried, and triturated with diethyl ether. The solid (m.p. 126–135°) is again recrystallized from ethanol to give 300 g. (65%) of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid, m.p. 144–146°. Recrystallization from dioxane and then from dimethylformamide raises the melting point to 147–148°.

N-Benzyl-N-methylacetamide from Benzene and N-Methyl-N-methylolacetamide with Boron Trifluoride.³² Through a stirred suspension of 20.6 g. (0.2 mole) of N-methyl-N-methylolacetamide in 100 ml. of dry benzene is passed a slow stream of boron trifluoride while the temperature is maintained at 60° by means of a cold water bath. When the mixture is saturated and no more heat is evolved, it is cooled in an ice bath, then poured into ice water and separated. The aqueous phase is extracted with diethyl ether, and the combined benzene and ether layers are dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate leaves an oil which is fractionally distilled to give 22.0 g. (68%) of N-benzyl-N-methylacetamide, b.p. 91–93°/0.2 mm., m.p. 40–41°.

N-(2'-Methyl-5'-nitrobenzyl)-2-pyrrolidinone from 4-Nitrotoluene, 2-Pyrrolidinone, and Paraformaldehyde in Concentrated Sulfuric Acid.³⁴ To 600 ml. of concentrated sulfuric acid maintained at 20° are added with stirring 274 g. (2.0 moles) of 4-nitrotoluene, 60 g. (2.0 moles) of paraformaldehyde, and 170 g. (2.0 moles) of 2-pyrrolidinone. The solution is allowed to stand at room temperature for 12–15 hours, then at 45° for 6 hours, and finally at 65° for 12 hours. It is then cooled and poured over ice, and the oily product is washed with water by decantation until free of acid. The washed oil is taken up in a minimum amount of warm carbon tetrachloride. The white crystals which deposit on cooling are collected and dried. There is obtained 174 g. (37%) of N-(2'-methyl-5'-nitrobenzyl)-2-pyrrolidinone, m.p. 94–96°.

N,N'-Diacyl-4,6-di(aminomethyl)-1,3-xylene from *m*-Xylene, Acetonitrile, and Formaldehyde in 85% Phosphoric Acid.⁵ In a 5-l. three-necked flask fitted with a Hershberg stirrer, condenser, and thermometer are placed 1.5 l. of 85% phosphoric acid, 360 g. (11 moles) of 91% paraformaldehyde, 530 g. (5.0 moles) of *m*-xylene, and 535 g. (13 moles) of acetonitrile. The mixture is heated with vigorous agitation to 65° whereupon a spontaneous reaction occurs. The temperature is held at 65–75° until the exothermic reaction is over, and then at 90° for 4 hours. After cooling there remains a layer of 124–135 g. of unchanged

xylene. The viscous acid layer is added in a slow stream with vigorous agitation to 8 l. of ice water containing 3 l. of concentrated ammonium hydroxide. The resulting suspension is stirred overnight, filtered, and the solid washed with dilute ammonium hydroxide and dried at 75° for 24 hours. The yield of crude diamide, m.p. 225–235°, is 600–611 g. (61–66% based on xylene converted). Recrystallization from methanol gives pure N,N'-diacetyl-4,6-di-(aminomethyl)-1,3-xylene, m.p. 245–246°.

N-(2-Hydroxy-3,5-dimethylbenzyl)-N'-phenylurea from 2,4-Xylenol and the Ether ($C_6H_5NHCONHCH_2$)₂O, in Formic Acid.⁵⁴ A solution of 0.9 g. of 2,4-xylenol and 0.7 g. of the ether in 20 ml. of formic acid is warmed at 50° for 2 hours, poured into water, and allowed to stand for 4 hours. The product is collected and dried. The yield is 90%. Recrystallization from benzene gives the pure diarylurea, m.p. 169°.

N-Benzylphthalimide from Benzene, N-Bromomethylphthalimide, and Zinc Chloride.¹⁴ A solution of 24 g. (0.1 mole) of N-bromomethylphthalimide in 50 ml. of dry benzene is treated with 1 g. of anhydrous zinc chloride and then heated under reflux for 2 hours or until the evolution of hydrogen bromide nearly ceases. The cooled red solution is poured into water, separated, and washed to neutrality with aqueous sodium bicarbonate and water. The organic layer is filtered to remove any insoluble material, and the filtrate is then concentrated. The residual solid (22.6 g., 94%, m.p. 110–113°) is recrystallized once from 100 ml. of ethanol to give 20.2 g. of N-benzylphthalimide, m.p. 113–114°.

2- and 4-Methoxybenzylamine from Anisole and N-Chloromethylphthalimide (Zinc Chloride Catalyst).^{37b} A mixture of 280 g. (2.9 moles) of anisole, 215 g. (1.1 moles) of N-chloromethylphthalimide, and 11 g. of anhydrous zinc chloride is heated for 2 hours at 120–140°. The excess anisole is removed by steam distillation, and the layer of water is decanted from the pasty residue which crystallizes after trituration with a little ethanol.

The mixture of N-(2- and 4-methoxybenzyl)phthalimide is collected and hydrolyzed directly by stirring it for 2–3 hours at room temperature with a mixture of 250 ml. of ethanol and 1.5 l. of 12% aqueous sodium hydroxide. The mixture is then concentrated under reduced pressure to two-thirds of its original volume and treated carefully with 700 ml. of concentrated hydrochloric acid. After the mixture has been heated on the steam bath for several hours, it is cooled, filtered to remove insoluble material, and the filtrate is concentrated to dryness. The residue is made alkaline with 35% sodium hydroxide solution, and the base which is released is taken up in benzene and dried over anhydrous potassium carbonate. Filtration, removal of the benzene, and distillation of the

⁵⁴ Shirakawa and Kawasaki, *J. Pharm. Soc. Japan*, 71, 1213 (1951) [*C.A.*, 46, 5544 (1952)].

residue under reduced pressure give a crude base, b.p. 120–140°/21 mm. Redistillation at atmospheric pressure gives 98 g. (65%) of a mixture of 2- and 4-methoxybenzylamine, b.p. 231–235°.

The mixture of amines is then added dropwise with stirring to 330 g. of 10% anhydrous ethanolic hydrogen chloride. After it has stood overnight at room temperature, the solid is collected, washed with 100 ml. of ethanol, and dried to give 73 g. (38%) of 4-methoxybenzylamine hydrochloride, m.p. 223–230°. Recrystallization from ethanol raises the melting point to 231–233°.

The alcoholic filtrate is concentrated to dryness under reduced pressure to give crude 2-methoxybenzylamine hydrochloride corresponding to a 19% yield based on the original N-chloromethylphthalimide. The crude product can be purified by solution in water and treatment with a hot aqueous solution of picric acid. The 2-methoxybenzylamine picrate, m.p. 227–228°, which is formed can be reconverted through the base, b.p. 120–122°/16 mm., to pure 2-methoxybenzylamine hydrochloride, m.p. 148–149° (from ethanol).

4-Phthalimidomethyl-1-naphthol-8-sulfonic Acid γ -Sultone from 1,8-Naphthsultone and N-Chloromethylphthalimide with Aluminum Chloride.⁷⁷⁹ A stirred mixture of 62 g. (0.3 mole) of 1,8-naphthsultone, 71 g. (0.36 mole) of N-chloromethylphthalimide, and 52 g. (0.39 mole) of anhydrous aluminum chloride in 500 ml. of 1,2,4-trichlorobenzene is slowly heated to 110° over a 2-hour period and then kept at that temperature for another 2 hours and 15 minutes. The cooled reaction mixture is poured over 500 g. of ice containing 30 ml. of concentrated hydrochloric acid, and the trichlorobenzene is removed by steam distillation. The glassy residue is boiled with 300 ml. of ethyl acetate, and the resulting crystalline solid is collected and washed successively with ethyl acetate and hot water. The dried product weighs 95 g. (97%), m.p. 248–249°. Recrystallization from a chloroform-ethanol mixture and then from glacial acetic acid gives pure 4-phthalimidomethyl-1-naphthol-8-sulfonic acid γ -sultone, m.p. 252–253°.

α -Benzoylamino- α -phenyl-*o*-cresol from Phenol and N,N'-Benzylidenebisbenzamide.⁷⁴ A mixture of 6.6 g. (0.02 mole) of the bisamide and 1.88 g. (0.02 mole) of phenol is heated for 4 hours at 180–190° in an oil bath. The brown, hard, resinous material is dissolved in glacial acetic acid, and the product is precipitated by the addition of water. The precipitate is collected, washed with water, and dried to give 4.2 g. (69%) of a yellow powder, m.p. 118°. The powder is dissolved in the minimum amount of ethyl acetate, filtered from a small quantity of insoluble material, and recovered once again by removal of the ethyl acetate. Four

⁷⁷⁹ Schetty, *Helv. Chim. Acta*, **31**, 1229 (1948).

recrystallizations from ethanol give pure α -benzoylamino- α -phenyl-*o*-cresol, m.p. 214°.

2-(α -Acetylaminobenzyl)-4-nitrophenol from 4-Nitrophenol, *N,N'*-Benzylidenebisacetamide, and Phosphorus Oxychloride.¹⁸ A mixture of 3.5 g. (0.025 mole) of 4-nitrophenol, 5.76 g. (0.028 mole) of the bisamide, and 1.84 g. (0.012 mole) of phosphorus oxychloride is heated (94–96°) on the steam bath for 1 hour. The cooled mixture is decomposed with water and neutralized with sodium bicarbonate. The resulting solid is collected, washed, and dried. Recrystallization from ethanol gives 5.8 g. (81 %) of pure 2-(α -acetylaminobenzyl)-4-nitrophenol, m.p. 208–209°.

α -Amidoalkylation of Aliphatic Carbon Atoms

2-Benzamidomethylcyclohexane-1,3-dione (50) from *N*-Methylolbenzamide and Cyclohexane-1,3-dione.⁸⁵ A solution of 2.24 g. (0.02 mole) of cyclohexane-1,3-dione and 3.02 g. (0.02 mole) of *N*-methylolbenzamide in 20 ml. of acetic acid is treated with 1.5 g. (0.01 mole) of boron trifluoride etherate. After 20 hours a first crop of crystals is obtained (scratching may be necessary) and collected. The filtrate is mixed with water containing 2.5 g. of sodium acetate, and a second crop of colorless crystals is obtained. The combined amount is 4.0 g. of crystals, m.p. 157–160°. The crude product is digested with 100 ml. of cold 1*N* sodium hydroxide and the insoluble by-product, methylenebisbenzamide, is removed by filtration. The filtrate is acidified with concentrated hydrochloric acid, and the resulting solid is collected and recrystallized from ethanol to give 3.2 g. (65 %) of pure product, m.p. 162–164°.

***N,N'*-Bis-(β -trinitroethyl)fumaramide (54)** from *N,N'*-Bis(benzoxymethyl)fumaramide and Trinitromethane.⁹³ A mixture of 50 ml. of dry nitromethane, 0.38 g. (1.0 mmole) of *N,N'*-bis(benzoxymethyl)fumaramide, and 0.45 g. (3.0 moles) of trinitromethane is heated under reflux for 4 hours. The solvent is then removed in vacuum, and the solid residue is extracted with boiling carbon tetrachloride in order to remove the benzoic acid. The residue, which is insoluble in carbon tetrachloride, is dissolved in absolute ethanol, and water is added to the point of turbidity. On standing, 0.20 g. (47 %) of product, m.p. 197° (dec.), crystallizes.

Diethyl Methylbenzamidomethylmalonate, $C_6H_5CONHCH_2-C(CH_3)(CO_2C_2H_5)_2$, from *N*-Chloromethylbenzamide and Diethyl Methylmalonate.¹⁰⁰ A suspension of 4.2 g. (0.025 mole) of *N*-chloromethylbenzamide and 4.7 g. (0.024 mole) of diethyl sodiomethylmalonate in 20 ml. of dry diethyl ether is heated on a steam bath under reflux for 1

hour. The slimy precipitate is removed by filtration and washed with ether. The ether fractions are combined, and the ether is removed by distillation. The viscous yellow residue is distilled under reduced pressure. Any unchanged diethyl methyl malonate distills as the oil bath is heated to 180°. The fraction distilling at 180°/0.05 mm. is collected, and it eventually crystallizes as a white, waxy substance. It is recrystallized from diisooamyl ether to give 5.8 g. (78%) of product, m.p. 67°.

Diethyl α -Acetamidobenzylmalonate, $\text{CH}_3\text{CONHCH}(\text{C}_6\text{H}_5)-\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$, from Benzylidenebisacetamide and Diethyl Malonate.¹¹⁵ A mixture of 10.3 g. (0.05 mole) of *N,N'*-benzylidenebisacetamide, 8 g. (0.05 mole) of diethyl malonate, and 25 ml. of acetic anhydride is heated for 3 hours in an oil bath at 150–155°. (Prolonged heating leads to diethyl benzylidenemalonate; e.g., after heating for 9 hours the yield drops to 11%.) The acetic anhydride is removed under reduced pressure (14 mm.), and 100 ml. of water is added with stirring to the remaining viscous mass. The colorless crystals that separate are collected and washed with cold water and a little diethyl ether. The dried product, m.p. 83°, weighs 8.9 g. An additional 0.7 g. is obtained from the ether filtrate (total yield: 9.6 g., 62%). Recrystallization from 50% ethanol gives the pure product, m.p. 85°. It is readily soluble in ethanol and acetone, sparingly soluble in ether, and insoluble in water.

Diethyl α -Benzamidomethyl- α -cyanopimelate (82) from *N*-(Diethylaminomethyl)benzamide and Diethyl α -Cyanopimelate.¹¹⁸ A mixture of 2.4 g. (0.01 mole) of diethyl α -cyanopimelate, 2.06 g. (0.01 mole) of *N*-(diethylaminomethyl)benzamide, 0.01 g. of powdered sodium hydroxide, and 30 ml. of toluene is heated at reflux under nitrogen. After 5 hours 80% of the theoretical quantity of diethylamine is evolved. The mixture is then cooled, and 100 ml. of petroleum ether is added. An oil separates which crystallizes after 3 days. This solid is recrystallized from petroleum ether to give 3.2 g. (85%) of the product 82, m.p. 61°.

β -Benzamido- β,β -diphenylpropionitrile from *N*-Benzoyldiphenylketimine and Acetonitrile.¹²⁰ To a stirred solution of 1.49 g. (0.065 mole) of lithium amide in 200 ml. of liquid ammonia is added, during 5 minutes, a solution of 1.25 g. (0.03 mole) of acetonitrile in 10 ml. of diethyl ether. The mixture is stirred for 15 minutes and then, over another 5 minute period, is added a solution of 8.60 g. (0.03 mole) of *N*-benzoyldiphenylketimine $[\text{C}_6\text{H}_5\text{CON}=\text{C}(\text{C}_6\text{H}_5)_2]$ in a mixture of benzene (100 ml.) and ether (50 ml.). After stirring for 1 hour, 3.50 g. of solid ammonium chloride is added, the ammonia is removed by distillation, and 100 ml. of water is added to the residue. The organic layer is separated, washed with water, and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent by distillation give 8.40 g.

(85%) of material, m.p. 132–134°. Recrystallization from ethanol gives pure product, m.p. 134–135°.

5-Carbethoxy-2-keto-6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidine (90) from Ethyl Acetoacetate, Benzaldehyde, and Urea.¹²³ A mixture of 53 g. (0.5 mole) of benzaldehyde, 30 g. (0.5 mole) of urea, 97.5 g. (0.75 mole) of ethyl acetoacetate, 200 ml. of absolute ethanol, and 40 drops of concentrated hydrochloric acid is heated under reflux for 3 hours. The mixture is then cooled to 0°, and the crystallized pyrimidine (93.6 g.) is collected and dried at 50°. The filtrate is heated under reflux for 2 hours and then distilled until 155 ml. of ethanol is collected. On cooling the residue an additional 21.3 g. of the pyrimidine is obtained, giving a total crude yield of 114.9 g. For purification the crude product is divided into two equal portions, and each is dissolved in 800 ml. of boiling 95% ethanol. On cooling, the pyrimidine separates to give 102 g. (78%) of colorless crystals, m.p. 202–204°. The loss on recrystallization may be materially decreased by distilling the solvent to incipient crystallization. The pyrimidine dissolves slowly in ethanol, and an excess of solvent is needed to effect solution.

Preparation of Some Electrophilic Reagents

N-Methyloltrifluoroacetamide, $\text{CF}_3\text{CONHCH}_2\text{OH}$.²³⁹ Trifluoroacetamide (4.4 g., 0.039 mole), potassium carbonate (0.16 g.), and formalin (3.2 ml., 0.042 mole) are mixed. A homogeneous solution forms, and the product crystallizes almost immediately. After refrigeration overnight the product is collected and recrystallized from chloroform to yield 4.95 g. (88%) of filamentary crystals. One more recrystallization from the same solvent gives N-methyloltrifluoroacetamide, m.p. 105–105.5°, with a satisfactory elemental analysis.

N-Methylolphthalimide.⁵⁴ A mixture of 511 g. (3.48 moles) of phthalimide, 260 ml. of 40% formaldehyde solution, and 1.75 l. of water is heated until a clear solution results. This requires only 5 minutes after the boiling point is reached. The solution is refrigerated overnight, the product is removed by filtration, washed with ice water, and air-dried. The yield of N-methylolphthalimide, m.p. 137–141°, is 594 g. (96%), and the product is sufficiently pure for most purposes. The material should not be dried at elevated temperatures because it loses formaldehyde. Recrystallization from ethanol does not improve the melting point.

If a pure sample is needed, the following procedure may be used.¹²⁷ A solution obtained by warming 17.7 g. of N-methylolphthalimide in 30 ml.

of pure pyridine is filtered, if necessary, and left to crystallize. If crystallization does not occur, seed crystals are obtained by placing a few drops of the solution in a desiccator over concentrated sulfuric acid. As soon as the first crystals appear, they are added to the solution. The pyridine complex crystallizes in long lustrous needles which are collected after cooling in an ice bath. On drying in vacuum over concentrated sulfuric acid, the crystals lose their luster and come to constant weight after 24 hours. The dried product melts at 148.5–149°, and one recrystallization from acetone gives pure *N*-methylolphthalimide, m.p. 149.5°.

***N*-Chloromethyltrichloroacetamide.**¹⁸⁶ A cold stirred solution of 19.2 g. (0.1 mole) of *N*-methyloltrichloroacetamide²⁸⁴ in 10 ml. of dry diethyl ether is treated with a suspension of 20 g. (0.096 mole) of phosphorus pentachloride in 20 ml. of dry diethyl ether. After the initial reaction and evolution of hydrogen chloride moderates, the mixture is heated for 10 minutes under reflux and allowed to stand overnight. Ice water is then added dropwise to the cooled, stirred solution. The precipitate is collected and washed with ice water. Two recrystallizations from lukewarm carbon tetrachloride give 16 g. (76%) of *N*-chloromethyltrichloroacetamide, m.p. 76–77°.

***N*-Bromomethylphthalimide.**¹⁰⁴ A mixture of 80 g. (0.45 mole) of *N*-methylolphthalimide, 150 ml. of 48% hydrobromic acid, and 45 ml. of concentrated sulfuric acid is stirred for 2 hours at 50–60°. The crystalline product is collected and washed with water and then with dilute aqueous ammonia to remove all acid. Drying at 80° gives 75 g. (69%) of *N*-bromomethylphthalimide, m.p. 146–147°. Recrystallization from acetone gives a purer product, m.p. 148°.

***N*-Acetoxymethylstearamide from Stearamide and Paraformaldehyde in Acetic Acid-Acetic Anhydride.**¹³⁸ A solution of 200 g. (0.71 mole) of stearamide and 25 g. (0.83 mole) of paraformaldehyde in a mixture of 200 ml. of acetic anhydride and 400 ml. of glacial acetic acid is heated at 70° for 4 hours and then cooled. The precipitate is collected and dried. Recrystallization from acetone gives *N*-acetoxymethylstearamide, m.p. 92–93°, in 66% yield.

***N,N'*-Methylenebis-*p*-toluamide from *p*-Tolunitrile.**⁴ A solution of trioxane (1.5 g., .05 mole) in *p*-tolunitrile (11.7 g., 0.1 mole) is added slowly with stirring to 38 ml. of an 85% solution of sulfuric acid in a 125-ml. three-necked flask. The temperature is maintained at 30° by means of an ice bath. After 3 hours the solution is poured into 300 ml. of ice and water. The product separates as white crystals which are collected, washed with water, and recrystallized from 95% ethanol. The yield of *N,N'*-methylenebis-*p*-toluamide, m.p. 209–210°, is 12.4 g. (83%).

N,N'-Methylenebischloroacetamide from N-Methylolchloroacetamide.¹¹ N-Methylolchloroacetamide (10 g., 0.081 mole) is dissolved in 25 g. of concentrated sulfuric acid with cooling. The solution is allowed to stand overnight and is then poured over ice. The precipitate is collected and the filtrate saturated with salt to obtain more of the product which is collected and combined with the main product. The yield of crude material is 95%. Recrystallization from 95% ethanol gives pure N,N'-methylenebischloroacetamide, m.p. 175°.

N,N'-Benzylidenebisacetamide.²⁸³ A solution of 10.6 g. (0.1 mole) of benzaldehyde and 11.8 g. (0.2 mole) of acetamide in 100 ml. of benzene is heated under reflux for 48 hours under a Soxhlet extractor containing 50 g. of anhydrous magnesium sulfate. The precipitate is filtered, washed with acetone, and recrystallized from ethanol to give a 72% yield of N,N'-benzylidenebisacetamide, m.p. 239.5°.

N,N'-Benzylidenebisbenzamide.⁸⁵ A mixture of freshly distilled benzaldehyde (21.2 g., 0.2 mole), benzamide (48.4 g., 0.4 mole), and freshly distilled acetic anhydride (50 ml.) is warmed until a clear solution results. Four drops of concentrated hydrochloric acid is added, and the solution is heated on a steam bath for 2 hours. The acetic anhydride is removed by distillation under reduced pressure, and the residue is taken up in hot ethanol. Cooling gives 51.7 g. (78%) of crystalline N,N'-benzylidenebisbenzamide, m.p. 231.5–232.5°.

Stearamidomethylpyridinium Chloride, $n\text{-C}_{17}\text{H}_{35}\text{CONHCH}_2^{\oplus}$ $\text{NC}_5\text{H}_5\text{Cl}^{\ominus}$.¹³⁸ Stearamide (141 g., 0.5 mole) and paraformaldehyde (20 g., 0.67 mole) are added to a solution of 0.5 mole of pyridine hydrochloride in 2 l. of pyridine. The mixture is heated at 80° for 10 hours, cooled, and filtered. An equal volume of cold acetone is added to the filtrate, and the precipitate is collected and added to the original crop. The combined solids are recrystallized from acetone to yield 160 g. (78%) of stearamidomethylpyridinium chloride, melting at about 135°. The material sinters at 92°, and the final melting point varies with the rapidity of heating, probably because of partial conversion to methylenedistearamide.

TABULAR SURVEY

The tables fall into three groups. Tables I to VII summarize the α -amidoalkylation reactions of aromatic carbon atoms, Tables VIII to XIX those involving substitution at aliphatic carbon atoms, and Tables XX to XXXVI list the various electrophilic reagents that have been used in the α -amidoalkylation of carbon atoms.

The literature has been surveyed through 1962, but a number of more recent references have been included in both the text and the tables.

Exhaustive coverage has been attempted for the first two parts of this survey, but no such claim can be made for the third. The widely dispersed way in which these compounds appear in the literature makes omission of many examples a virtual certainty. Sufficient numbers have been listed, however, to provide a representative sampling of possible structural variation in the electrophilic reagent.

Because the N-aminomethylamides have been thoroughly reviewed recently,³ Table XXVIII is intentionally incomplete. It is devoted exclusively to examples which were omitted from the review cited or which have been reported since its publication.

Within each table, reactions or reagents are arranged in order of increasing complexity of the amide portion of the amidoalkylating reagent. The nucleophilic substrates are generally arranged according to increasing complexity of substituent groups as listed in Heilbron's *Dictionary of Organic Compounds*.^{3a1} Where applicable, the order aliphatic, aromatic, heterocyclic is also followed, but arylaliphatic aldehydes, acids, and amides are treated as derivatives of the aliphatic portion of the molecule. Compounds containing reactive methylene or methine groups are listed in the order nitro, aldehydo, keto, ester, polynitro, diketone, nitro ester, keto ester, diester, cyano, cyano ketone, and cyano ester.

Except where a separate column is provided for them, yields are given in parentheses after the references to which they relate.

^{3a1} Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, pp. xv-xvi.

TABLE I
 ANNOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF
 CARBOXAMIDES AND CARBAMYL COMPOUNDS
 $\text{RCONHCH}_2\text{OH} + \text{ArH} \rightarrow \text{RCONHCH}_2\text{Ar}$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$\text{HCONHCH}_2\text{OH}$ and 4-Nitrophenol	<i>o</i> -	Concd. H_2SO_4	22
$\text{CH}_3\text{CONHCH}_2\text{OH}$ and 4-Nitrophenol	<i>o</i> , <i>o</i> '-	Concd. H_2SO_4	23
2-Naphthol	1-	HCl , $\text{C}_2\text{H}_5\text{OH}$	96 (95)
Thiophene	2-	85 % H_3PO_4 , 90°	49 (50)
Ethyl 2,5-dimethylpyrrolo-3-carboxylate	4-	HCl , $\text{C}_2\text{H}_5\text{OH}$	17
$\text{CH}_3\text{CON}(\text{CH}_3)\text{CH}_2\text{OH}$ and Benzene	1-	BF_3 , C_6H_6	32 (68)
2-Naphthol	1-	HCl , $\text{C}_2\text{H}_5\text{OH}$	32 (94)
$\text{CH}_3\text{CON}(\text{C}_3\text{H}_7)_2\text{CH}_2\text{OH}$ and 2-Naphthol	1-	HCl , $\text{C}_2\text{H}_5\text{OH}$	32
$\text{CH}_3\text{ClCONHCH}_2\text{OH}$ and Benzene	1-	Concd. H_2SO_4	13 (88)
Chlorobenzene	2- and 4-	Concd. H_2SO_4	13 (80)
Phenol	4-	AlCl_3 , $\text{CH}_3\text{CO}_2\text{H}$	51
2-Nitrophenol	4-	Concd. H_2SO_4	11 (90)
4-Nitrophenol	2-	Concd. H_2SO_4	11 (90), 20
Catechol	<i>o</i> -	3 % HCl , H_2O	11
Hydroquinone	<i>o</i> , <i>o</i> '-	1 % HCl , $\text{C}_2\text{H}_5\text{OH}$	11 (20)
Pyrogallol	<i>o</i> , <i>o</i> '-	1 % HCl , $\text{C}_2\text{H}_5\text{OH}$	11 (15)

4-Nitrophenetole	2,6-	Concd. H ₂ SO ₄	11 (80)
Guaiacol	4-	20 % H ₂ SO ₄ , C ₂ H ₅ OH	11, 382
	4-	AlCl ₃ , CH ₃ CO ₂ H	51 (64)
Veratrole	4- and 2,4-	ZnCl ₂ , CH ₃ CO ₂ H	52
1,2,3-Trimethoxybenzene	4-	ZnCl ₂ , CH ₃ CO ₂ H	52
1,2,4-Trimethoxybenzene	5-	ZnCl ₂ , CH ₃ CO ₂ H	52
Acetanilide	4-	Concd. H ₂ SO ₄	11 (100), 20
4-Hydroxyacetanilide	3-	AlCl ₃ , CH ₃ CO ₂ H	51 (16)
Acetophenetidine	x-	Concd. H ₂ SO ₄	11 (70)
4-(CH ₃ CHOHCONH)C ₆ H ₄ OC ₂ H ₅	x-	Concd. H ₂ SO ₄	11 (70)
Toluene	4-	H ₂ SO ₄ , CH ₃ CO ₂ H	13 (75)
	4-	70 % H ₂ SO ₄	13 (50)
	2,4-	Concd. H ₂ SO ₄	13 (47)
m-Xylene	4-	H ₂ SO ₄ , CH ₃ CO ₂ H	13 (94)
p-Xylene	4,6-	Concd. H ₂ SO ₄	13 (35)
Thymol	2-	H ₂ SO ₄ , CH ₃ CO ₂ H	13 (92)
Phenylacetic acid	x-	1 % HCl, C ₂ H ₅ OH	11 (20)
Cinnamic acid	4-	Concd. H ₂ SO ₄ or HF	47 (35)
Benzoic acid	3- and 4-	Concd. H ₂ SO ₄	21 (68)
2-Chlorobenzoic acid	3-	Concd. H ₂ SO ₄	11 (54), 20
Salicylic acid	5-	Concd. H ₂ SO ₄	57 (65)
3,4,5-Trimethoxybenzoic acid	x,x-	Concd. H ₂ SO ₄	11 (40), 20
o-Toluic acid	2-	ZnCl ₂ , CH ₃ CO ₂ H	52
p-Toluic acid	5(7)-	Concd. H ₂ SO ₄	7
Tetralin	3-	Concd. H ₂ SO ₄	7
Naphthalene	x-	H ₂ SO ₄ , CH ₃ CO ₂ H	13 (39)
	x,x-	Concd. H ₂ SO ₄	13 (46)
	x-	H ₂ SO ₄ , CH ₃ CO ₂ H	13 (85)
2-Naphthol	x,x,x-	Concd. H ₂ SO ₄	13 (28)
2-Methoxynaphthalene	1-	Satd. HCl, C ₂ H ₅ OH	26 (81)
	1-	Satd. HCl, C ₂ H ₅ OH	26 (60)

Note. References 382 to 537 are on pp. 260-269.

TABLE I—Continued

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES AND CARBAMYL COMPOUNDS

$\text{RCONHCH}_2\text{OH} + \text{ArH} \rightarrow \text{RCONHCH}_2\text{Ar}$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$\text{CH}_3\text{C(RCONHCH}_2\text{OH (contd.) and$			
1-Hydroxy-2-naphthoic acid	4-	$\text{H}_2\text{SO}_4, \text{CH}_3\text{CO}_2\text{H}$	40
2-Hydroxy-3-naphthoic acid	1-	$\text{H}_2\text{SO}_4, \text{CH}_3\text{CO}_2\text{H}$	40
9-Fluorenone	2,7-	Concd. H_2SO_4	7
2-Nitro-9-fluorenone	7-	Concd. H_2SO_4	7
9,10-Phenanthrenequinone	2(?)	Concd. H_2SO_4	7
7H-Benz[de]anthracen-7-one (benzanthrone)	3,9(?)	Concd. H_2SO_4	7
Methyl 2-furoate	5-	Concd. H_2SO_4	35 (100)
Ethyl 2-furoate	5-	Concd. H_2SO_4	383
	5-	PPA, * $\text{CH}_3\text{CO}_2\text{H}$	48 (51)
2-Thiophenecarboxylic acid	4(?)	Concd. H_2SO_4	56 (53)
Ethyl 2,4-dimethylpyrrole-3-carboxylate	5-	$\text{HCl}, \text{C}_2\text{H}_5\text{OH}$	17 (good)
Ethyl 2,5-dimethylpyrrole-3-carboxylate	4-	$\text{HCl}, \text{C}_2\text{H}_5\text{OH}$	17 (good)
Acridine	2-	Concd. H_2SO_4	384
3-Methyl-1-phenyl-5-pyrazolone	4-	Concd. H_2SO_4	11
2,3-Dimethyl-1-phenyl-5-pyrazolone (antipyrine)	4-	$\text{AlCl}_3, \text{CH}_3\text{CO}_2\text{H}$	51 (70)
	4-	100 % $\text{H}_3\text{PO}_4, \text{CH}_3\text{CO}_2\text{H}$	48 (48)
$\text{CCl}_3\text{CONHCH}_2\text{OH and}$			
2-Hydroxybenzophenone	3,5(?)	Concd. H_2SO_4	7
4-Hydroxybenzophenone	3,5(?)	Concd. H_2SO_4	7
2,4-Dimethylbenzophenone	5(?)	Concd. H_2SO_4	7
<i>o</i> -Toluic acid	5(?)	Concd. H_2SO_4	7
<i>p</i> -Toluic acid	3-	Concd. H_2SO_4	7
2,4-Dimethylbenzoic acid	5-	Concd. H_2SO_4	7

9-Fluorenone	2,7-	Concd. H ₂ SO ₄	7
2-Nitro-9-fluorenone	7-	Concd. H ₂ SO ₄	7
2-Hydroxy-9-fluorenone	7-	Concd. H ₂ SO ₄	7
2-Acetyl-9-fluorenone	7-	Concd. H ₂ SO ₄	7
1,2-Acenaphthenequinone	4-	Concd. H ₂ SO ₄	7
1-Hydroxyanthraquinone	4-	Concd. H ₂ SO ₄	385
2-Hydroxyanthraquinone	1-	Concd. H ₂ SO ₄	37, 385, 386
2-Hydroxy-1-chloroanthraquinone	3-	Concd. H ₂ SO ₄	39
2-Hydroxy-3-chloroanthraquinone	1-	Concd. H ₂ SO ₄	37, 387
1,2-Dihydroxyanthraquinone	2,4,6,8-	Concd. H ₂ SO ₄	36, 37
1,5-Dihydroxyanthraquinone	2,4,5,7-	Concd. H ₂ SO ₄	385
1,8-Dihydroxyanthraquinone	1,4-	Concd. H ₂ SO ₄	385
2,3-Dihydroxyanthraquinone	4-	Concd. H ₂ SO ₄	37, 385
1-Hydroxy-2-methylanthraquinone	1-	Concd. H ₂ SO ₄	37, 385
2-Hydroxy-3-methylanthraquinone	4-	Concd. H ₂ SO ₄	37, 385
1,3-Dimethylanthraquinone	1-	Concd. H ₂ SO ₄	7
2-Hydroxyanthraquinone-3-carboxylic acid	2(?) and 2,7(?)	Concd. H ₂ SO ₄	385
9,10-Phenanthrenequinone	7(?)	Concd. H ₂ SO ₄	7
2-Nitro-9,10-phenanthrenequinone	7(?) and 3,7(?)	Concd. H ₂ SO ₄	7
2-Hydroxy-9,10-phenanthrenequinone	3,9(?)	Concd. H ₂ SO ₄	7
7H-Benz[de]anthracene-7-one (benzanthrone)	9(?)	Concd. H ₂ SO ₄	7
3-Bromo-7H-benz[de]anthracene-7-one	9(?)	Concd. H ₂ SO ₄	7
3-Nitro-7H-benz[de]anthracene-7-one	2(?) and 2,4,5,7(?)	Concd. H ₂ SO ₄	7
Xanthone 9-one		Concd. H ₂ SO ₄	7
C ₆ H ₅ CH ₂ CONHCH ₂ CONHCH ₂ OH and p-Cresol	2-	1% HCl, C ₂ H ₅ OH	79
2-Naphthol	1-	HCl, C ₂ H ₅ OH	79
C ₆ H ₅ CONHCH ₂ CONHCH ₂ OH and 2-Naphthol	1-	HCl, C ₂ H ₅ OH	79

Note: References 382 to 537 are on pp. 260-269.

*Polyphosphoric acid.

TABLE I—Continued

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES AND CARBAMYL COMPOUNDS

$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$C_6H_5CH_2CONHCH_2OH$ and N,N-Dimethylaniline	4(?)	HCl, C_2H_5OH	388
p-Cresol	2-	1% HCl, C_2H_5OH	79
2-Naphthol	1-	1% HCl, C_2H_5OH	388 (84)
6-Bromo-2-naphthol	1-	1% HCl, C_2H_5OH	388 (85)
3,6-Dibromo-2-naphthol	1-	HCl, C_2H_5OH	388 (80)
$C_6H_5CH_2CONHCH(CH_3)CONHCH_2OH$ and 2-Naphthol	1-	HCl, C_2H_5OH	79
$C_6H_5CH_2CH_2CONHCH_2OH$ and 2-Naphthol	1-	HCl, C_2H_5OH	79
N-Methylol-2-pyrrolidinone and 2-Naphthol	1-	HCl, C_2H_5OH	33 (50)
$(CH_3)_2CHCH_2CONHCH_2OH$ and 2,4-Xylenol	6-		54
3,3-Bis(p-hydroxyphenyl)oxindole (phenolisin)	α - and α,α -	$ZnCl_2$, CH_3CO_2H	53
n- $C_7H_{15}CONHCH_2OH$ and 3,3-Bis(p-hydroxyphenyl)oxindole (phenolisin)	α - and α,α -	$ZnCl_2$, CH_3CO_2H	53
3,3-Bis(p-hydroxyphenyl)phthalide (phenolphthalein)	α,α -	$ZnCl_2$, CH_3CO_2H , 50°	53

n-C ₈ H ₁₇ CONHCH ₂ OH and Phenol	4(1)-	AlCl ₃ , CH ₃ CO ₂ H	51 (63)
Guaiacol	4-	AlCl ₃ , (CH ₃) ₂ CO	51 (73)
n-C ₉ H ₁₉ CONHCH ₂ OH and Guaiacol	4-	AlCl ₃ , CH ₃ CO ₂ H	51 (65)
	4-	100 % H ₃ PO ₄ , (CH ₃) ₂ CO	48 (61)
CH ₂ =CH(CH ₂) ₈ CONHCH ₂ OH and Catechol	4-	HCl, C ₂ H ₅ OH	389 (2)
Guaiacol	4-	20 % H ₂ SO ₄ , C ₂ H ₅ OH	382, 390
CH ₃ CH=CHCH ₂ CONHCH ₂ OH and Catechol	4-	AlCl ₃ , CH ₃ CO ₂ H	51 (63)
C ₆ H ₅ CONHCH ₂ OH and Benzene	4-	HCl, C ₂ H ₅ OH	389 (57)
Phenol	1-	H ₂ SO ₄ , CH ₃ CO ₂ H	13
	1,4-	Concd. H ₂ SO ₄	13 (32)
2-Nitrophenol	4(1)-	AlCl ₃ , (CH ₃) ₂ CO	51 (60)
4-Nitrophenol	4(1)-	100 % H ₃ PO ₄ , CH ₃ CO ₂ H	48 (66)
	4-	Concd. H ₂ SO ₄	10
	2-	Concd. H ₂ SO ₄	1,10 (90), 20
	2-	HCl, C ₂ H ₅ OH	1 (<90), 20
	2-	ZnCl ₂ , CH ₃ CO ₂ H	1 (<90), 20
	α-	HCl, C ₂ H ₅ OH	10 (30)
	2-	HCl, C ₂ H ₅ OH	10 (20)
	α,α-	HCl, C ₂ H ₅ OH	10 (33)
	4-	HCl, C ₂ H ₅ OH	10 (<25), 382 (27)
4-Nitroveratrole	4-	AlCl ₃ , (CH ₃) ₂ CO	51 (68)
1,2,3-Trinitroxybenzene	5-	Concd. H ₂ SO ₄	58 (31)
	4,5-	Concd. H ₂ SO ₄	52
	4- and 4,5-	ZnCl ₂ , CH ₃ CO ₂ H	52

Note: References 382 to 537 are on pp. 266-269.

TABLE I.—*Continued*

AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF CARBONAMIDES AND CARBAMYL COMPOUNDS

$RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$C_6H_5CONHCH_2OH$ (<i>contd.</i>) and			
N,N-Dimethylaniline	4-	HCl, C_2H_5OH	388 (26)
Acetanilide	3-	Concd. H_2SO_4	13 (82)
Toluene	4-	H_2SO_4 , CH_3CO_2H	13 (90)
p-Cresol	2-	HCl, C_2H_5OH	79
2,4-Xylenol	6-	HCl, C_2H_5OH	55
Thymol	3-	H_2SO_4 , C_2H_5OH	10 (62)
Benzoic acid	3-	Concd. H_2SO_4	10 (8), 20
o-Toluic acid	5(?)	Concd. H_2SO_4	7
p-Toluic acid	3-	Concd. H_2SO_4	7
1-Hydroxyphenylarsonic acid	3-	Concd. H_2SO_4	391
2-Naphthol	1-	HCl, C_2H_5OH	1, 10 (100), 20
6-Bromo-2-naphthol	1-	HCl, C_2H_5OH	388 (90)
3,6-Dibromo-2-naphthol	1-	HCl, C_2H_5OH	388
2-Methoxynaphthalene	1-	HCl, C_2H_5OH	392 (97)
2-Hydroxy-3-naphthoic acid	1-	HCl, CH_3OH , 40°	40
Fluorene		H_2SO_4 , CH_3CO_2H	86
9-Fluorenone	2,7-	Concd. H_2SO_4	7
1-Hydroxyanthraquinone	4- and 2,4-	Concd. H_2SO_4	37, 385
2-Hydroxyanthraquinone	1-	Concd. H_2SO_4	36, 37, 385
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	37
1,8-Dihydroxyanthraquinone	2,4,5-	Concd. H_2SO_4	385
1,3-Dimethylanthraquinone		Concd. H_2SO_4	7 (0)
2-Hydroxy-9,10-phenanthrenequinone	7(?)	Concd. H_2SO_4	7

7H-Benz[de]anthracen-7-one (benzanthrone)	3-	Concd. H_2SO_4	7
2-Furoic acid	5-	Concd. H_2SO_4	393 (30)
Methyl 2-furoate	5-	Concd. H_2SO_4	35 (100)
Ethyl 2-furoate	5-	Concd. H_2SO_4	383
2-Thiophenecarboxylic acid	4-	Concd. H_2SO_4	56
6-Hydroxyquinoline	x-	Concd. H_2SO_4	394
8-Hydroxyquinoline	x-	Concd. H_2SO_4	10, 394
2-Hydroxy-6-methoxy-4-methylquinoline	x-	Concd. H_2SO_4	394
Carbazole			86
Acridino	x-	Concd. H_2SO_4	384
Rhodanine			86
2,3-Dimethyl-1-phenyl-5-pyrazolone (antipyrene)	4-	$AlCl_3, (CH_3)_2CO$	51 (52)
Pterolic acid	4-	Concd. H_2SO_4	86
4-Methyl-2-thiouracil	5-	Concd. H_2SO_4	86
$o-O_2NC_6H_4CONHCH_2OH$ and 2-Furoic acid			395
$o-HOC_6H_4CONHCH_2OH$ and Catechol	5-	Concd. H_2SO_4	393
Hydroquinone	x,x-	HCl, C_2H_5OH	25 (50)
Pyrogallol	x,x-	HCl, C_2H_5OH	25 (50)
Phenetole	x-	HCl, C_2H_5OH	25 (100)
Thymol	4-	$AlCl_3, CH_3CO_2H$	51 (63)
$p-CH_3C_6H_4CONHCH_2OH$ and 2-Furoic acid	x-	HCl, C_2H_5OH	25 (50)
N-Methylol-2-furamide and N-Methylol-2-furamide	5-	Concd. H_2SO_4	393
	2,5-Polymer	Heat, pressure	35

Note: References 382 to 537 are on pp. 268-269.

TABLE I—*Continued*
 AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF
 CARBOXAMIDES AND CARBAMYL COMPOUNDS
 $RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylol- β -2-furamacylamide and N-Methylol- β -2-furamacylamide	2,5-Polymer	Heat, pressure	35
$C_6H_5O_2NCHCH_2OH$ and 2,4-Xylenol	6-	HCl, C_3H_5OH	218 (56)
$(CH_3)_2NCONHCH_2OH$ and 3,3-Bis(<i>p</i> -hydroxyphenyl)oxindole (phenolisation)	3,3'-	$ZnCl_2$, CH_3CO_2H , 50°	53
$CO(NHCH_2OH)_2$ † and Phenol	2-	HCl	38 (50)
2-Nitrophenol	4-	H_2SO_4 , CH_3CO_2H	40
4-Nitrophenol	2-	H_2SO_4 , CH_3CO_2H	40
1-Hydroxyanthraquinone	2-	Concd. H_2SO_4	37
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	36, 37, 39
$C_6H_5NCHONHCH_2OH$ and 2,4-Xylenol	6-	HCO_2H , 50°	54
p - $CH_3C_6H_4NCHONHCH_2OH$ and 2,4-Xylenol	6-	HCO_2H , 50°	55

Note: References 382 to 537 are on pp. 260-269.

† Reacting as a monomethylamide. For bifunctional reactions see Table III.

TABLE II
AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-METHYLOLIMIDES

Product Derived from	Position(s) of Substituent(s)	Method	Reference (Yield, %)
N-Methylsuccinimide and 4-Nitroveratrole	5-	Concd. H_2SO_4	58 (1.4)
N-Methylmaleimide and 2-Nitrotoluene	1(?)	Concd. H_2SO_4	8 (12)
N-Methylsuccinimide and 4-Methyl-2-thiourea	5-	Concd. H_2SO_4	395
N-Methylphthalimide and Benzene	1-	Concd. H_2SO_4	16
Nitrobenzene	3-	Oleum	16
Phenol	3,5-	20 % Oleum	29
4-Nitrophenol	4-	Concd. H_2SO_4	16
2,4-Dinitrophenol	2, 4-, and 2,4-	Concd. H_2SO_4	15
4-Nitroveratrole	2-	Concd. H_2SO_4	16
Aniline	6-	5 % Oleum, 95 %	69 (95)
N,N-Dimethylaniline	5-	Concd. H_2SO_4	58 (88)
Acetanilide	3- and 4-	4 % Oleum	14 (>60)
	5-	Concd. H_2SO_4	16
	4(?)	95 % H_2SO_4	396 (41)
	2- (27 %) and 4- (60 %)	99.5 % H_2SO_4	44 (87)
	2- (15 %), 4- (33 %), and 2,4- (27 %)	1.5 % Oleum	44 (75)
2-Nitrotoluene	4- (6 %) and 2,4- (66 %)	4 % Oleum	14 (72)
3-Nitrotoluene	5(?)	Concd. H_2SO_4	16 (95)
4-Nitrotoluene	5-	Concd. H_2SO_4	16
<i>o</i> -Toluidine	5-	Concd. H_2SO_4	16
	2,6-	Concd. H_2SO_4	29 (95)
	3,5-	Concd. H_2SO_4	29 (77)

Note: References 382 to 537 are on pp. 266-269.

TABLE I—Continued
 AMBOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-MONOMETHYLOL DERIVATIVES OF
 CARBOXAMIDES AND CARBAMYL COMPOUNDS
 $RCONHCH_2OH + ArH \rightarrow RCONHCH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylol- β -2-furanylamide and N-Methylol- β -2-furanylamide	2,5-Polymer	Heut, pressure	35
$C_6H_5O_2CNHCH_2OH$ and 2,4-Xylenol	6-	HCl, C_2H_5OH	218 (56)
$(CH_3)_2NCONHCH_2OH$ and 3,3-Bis-(<i>p</i> -hydroxyphenyl)oxindole (phenolatin)	3,3'-	$ZnCl_2$, CH_3CO_2H , 50°	53
$CO(NHCH_2OH)_2$ † and Phenol	2-	HCl	38 (50)
2-Nitrophenol	4-	H_2SO_4 , CH_3CO_2H	40
4-Nitrophenol	2-	H_2SO_4 , CH_3CO_2H	40
1-Hydroxyanthraquinone	2-	Concd. H_2SO_4	37
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	36, 37, 39
$C_6H_5NHCONHCH_2OH$ and 2,4-Xylenol	0-	HCO_2H , 50°	54
<i>p</i> - $CH_3C_6H_4NHCONHCH_2OH$ and 2,4-Xylenol	0-	HCO_2H , 50°	55

Note: References 382 to 537 are on pp. 260–260.

† Reacting as a monomethylamide. For bifunctional reactions see Table III.

TABLE II
AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-METHYLOLIMIDES

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylolsuccinimide and 4-Nitroveratrole	5-	Concd. H ₂ SO ₄	58 (1.4)
N-Methylolmaleimide and 2-Nitrotoluene	4(?)	Concd. H ₂ SO ₄	8 (12)
N-Methylolsaccharin and 4-Methyl-2-thiouracil	5-	Concd. H ₂ SO ₄	395
N-Methylolphthalimide and Benzene	1-	Concd. H ₂ SO ₄	16
Nitrobenzene	3-	Oleum	16
	3,5-	20 % Oleum	29
Phenol	4-	Concd. H ₂ SO ₄	16
4-Nitrophenol	2-, 4-, and 2,4-	Concd. H ₂ SO ₄	15
2,4-Dinitrophenol	2-	Concd. H ₂ SO ₄	16
4-Nitroveratrole	6-	Concd. H ₂ SO ₄	69 (95)
Aniline	5-	5 % Oleum, 95°	58 (88)
N,N-Dimethylaniline	3- and 4-	Concd. H ₂ SO ₄	44 (>60)
Acetanilide	2-	Concd. H ₂ SO ₄	16
	4(?)	95 % H ₂ SO ₄	396 (41)
	2- (27 %) and 4- (60 %)	99.5 % H ₂ SO ₄	44 (87)
	2- (15 %), 4- (33 %), and 2,4- (27 %)	1.5 % Oleum	44 (75)
	4- (6 %) and 2,4- (66 %)	4 % Oleum	44 (72)
2-Nitrotoluene	5(?)	Concd. H ₂ SO ₄	16 (95)
3-Nitrotoluene	2-	Concd. H ₂ SO ₄	16
4-Nitrotoluene	2-	Concd. H ₂ SO ₄	16
o-Toluidine	2,6-	Concd. H ₂ SO ₄	29 (95)
	3,5-	Concd. H ₂ SO ₄	29 (77)

Note: References 382 to 537 are on pp. 260-269.

TABLE II—*Continued*
 AMPDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-METHYLOLIMIDES

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Methylolphthalimide (<i>contd.</i>) and <i>p</i> -Toluidine	3-	98.3 % H_2SO_4	44 (81)
	3,5-	Concd. H_2SO_4	29 (95)
4-Methylacetanilide	2- (3 %) and 3- (17 %)	99.5 % H_2SO_4	44 (>20)
	2- (23 %) and 3- (55 %)	97.7 % H_2SO_4	44 (>78)
2,4-Nyldine	3,5-	90 % H_2SO_4	29
4-Phenylphenol	2-	H_2SO_4 , C_6H_6	397 (>30)
4-Hydroxyacetophenone	3-	Concd. H_2SO_4	69 (92)
2-Methylbenzophenone	3,5(?)	Concd. H_2SO_4	7
4-Methylbenzophenone	3(?)	Concd. H_2SO_4	7
2,4-Dimethylbenzophenone	5(?) and 3,5(?)	Concd. H_2SO_4	7
Phenylacetic acid	3- and 4-	Concd. H_2SO_4	47 (85)
Benzoic acid	3-	95 % H_2SO_4	396 (40)
	3-	Concd. H_2SO_4	12 (60)
	3-	Concd. H_2SO_4	7
<i>o</i> -Tolnic acid	5(?)	Concd. H_2SO_4	7
<i>m</i> -Tolnic acid	6-	Concd. H_2SO_4	7
<i>p</i> -Tolnic acid	3-	Concd. H_2SO_4	7
4- $\text{HOC}_6\text{H}_4\text{AsO}_3\text{H}$	3-	Concd. H_2SO_4	398
2-Naphthol	1-	88 % H_2SO_4	396 (53)
9-Fluorenone	2,7-	Concd. H_2SO_4	7
1-Hydroxyanthraquinone	2,4-	Concd. H_2SO_4	37, 385
2-Hydroxyanthraquinone	1-	Concd. H_2SO_4	36, 37, 385
2-Hydroxy-3-chloranthraquinone	1-	Concd. H_2SO_4	387
1,2-Dihydroxyanthraquinone	3-	Concd. H_2SO_4	37, 39
1,5-Dihydroxyanthraquinone	4(?)	Concd. H_2SO_4	385
1,8-Dihydroxyanthraquinone	2,4,5,7-	Concd. H_2SO_4	385
2,3-Dihydroxyanthraquinone	1,4-	Concd. H_2SO_4	385
1,4-Di-(4'-methylamino)anthraquinone	3', 5', 3'', 5'(?)-	96 % H_2SO_4	399 (97)
1-Amino-2-bromo-4-(4'-methylamino)-anthraquinone	3'(?)- and 3', 5'(?)-	96 % H_2SO_4	399 (100)

1,4,5,8-Tetra-(4'-methylamino)anthraquinone	3', 5', 3'', 5'', 3''', 5'''	98 % H ₂ SO ₄	399 (97)
1-Hydroxy-2-methylanthraquinone	4-	Concd. H ₂ SO ₄	37, 385
2-Hydroxy-3-methylanthraquinone	1-	Concd. H ₂ SO ₄	37, 385
1,3-Dimethylanthraquinone	4-	Concd. H ₂ SO ₄	7
2-Hydroxyanthraquinone-3-carboxylic acid	1-	Concd. H ₂ SO ₄	385
1-(2'-Methyl-5'-chloroanilino)anthraquinone-2-carboxylic acid	4'(?)	96 % H ₂ SO ₄	399 (95)
1-Amino-4-(4'-methylamino)-anthraquinone-2-sulfonic acid	3'(?)	96 % H ₂ SO ₄	399
9,10-Phenanthrenequinone	2(?) and 2,7(?)	Concd. H ₂ SO ₄	7
2-Hydroxy-9,10-phenanthrenequinone	7(?) and 3,7(?)	Concd. H ₂ SO ₄	7
2-Acetyl-9,10-phenanthrenequinone	7(?)	Concd. H ₂ SO ₄	7
7H-Benz[de]anthracen-7-one (benzanthrone)	3(?)	96 % H ₂ SO ₄	400, 401 (100)
	3,9(?)	Concd. H ₂ SO ₄	7
	3,9(?)	96 % H ₂ SO ₄ , 80°	400 (97)
	9(?)	96 % H ₂ SO ₄ , 80°	7, 400
3-Bromo-7H-benz[de]anthracen-7-one	3,3'(?)	96 % H ₂ SO ₄	402 (100)
			400 (95)
4,4'-Bis-7H-benz[de]anthracen-7-one	12(?)	10 % Oleum, 60°	403 (93)
Dibenz[ah]pyrene-7,14-dione (Indanthrene Golden Yellow GK)	10(?)	10 % Oleum, 60°	403
Dibenz[cd, jk]pyrene-6,12-dione (anthanthrone)	3(?)	10 % Oleum	403 (100)
Dinaphtho[1,2,3-cd : 3',2',1'-lm]perylene-5,10-dione (violanthrone)	5-	Concd. H ₂ SO ₄	383
Ethyl 2-furoate	5-	Concd. H ₂ SO ₄	395
4-Methyl-2-thiouracil	5-(21 %) and 8-(20 %)	Concd. H ₂ SO ₄	404 (41)
Quinoline	x,x-	100 % H ₂ SO ₄ , 75°	405
Cobalt phthalocyanine	x,x- to 8x	3 % Oleum, 100°	64
Copper phthalocyanine		H ₂ SO ₄ , H ₃ PO ₄ , or P ₂ O ₅	50
Cobalt monochlorophthalocyanine		100 % H ₂ SO ₄ , 75°	405

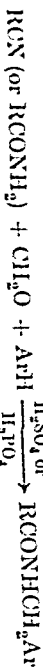
Note: References 382 to 537 are on pp. 266-269.
 * Sulfonation also occurred in the 12(?) position.

TABLE III
AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N,N'-DIMETHYLOL
DERIVATIVES OF DICARBOXYAMIDES AND OF UREA
 $(\text{CH}_2)_n(\text{CONHCH}_2\text{OH})_2 + 2\text{ArH} \rightarrow (\text{CH}_2)_n(\text{CONHCH}_2\text{Ar})_2$
and
 $\text{CO}(\text{NHCH}_2\text{OH})_2 + 2\text{ArH} \rightarrow \text{CO}(\text{NHCH}_2\text{Ar})_2$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$(\text{CONHCH}_2\text{OH})_2$ and Methyl 2-furoate Ethyl 2-furoate	5- 5-	Concd. H_2SO_4 Concd. H_2SO_4	35 (88) 35 (92)
$(\text{CH}_2)_3(\text{CONHCH}_2\text{OH})_2$ and 4-Nitrophenol 2,4-Xylenesulfonic acid 2-Naphthol	2- a- 1-	Concd. H_2SO_4 Concd. H_2SO_4 HCl , $\text{C}_3\text{F}_7\text{OH}$	20, 24 20 20, 24
$(\text{CH}_2)_4(\text{CONHCH}_2\text{OH})_2$ and Benzene 4-Nitrophenol Acetanilide 2-Methylacetanilide 4-Methylacetanilide 2-Naphthol 2-Acetylamino-naphthalene	1- 2- 4- a- a- 1- a-	Concd. H_2SO_4 Concd. H_2SO_4 Concd. H_2SO_4 Concd. H_2SO_4 Concd. H_2SO_4 Concd. H_2SO_4 Concd. H_2SO_4	406 406 (80) 406 (41) 406 406 (55) 406 (50) 406
$(\text{CH}_2)_7(\text{CONHCH}_2\text{OH})_2$ and Benzene	1-	Concd. H_2SO_4	406 (37)
$(\text{CH}_2)_8(\text{CONHCH}_2\text{OH})_2$ and Benzene	1-	Concd. H_2SO_4	406 (48)

TABLE IV

AROMATIZATION OF AROMATIC CARBON ATOMS WITH FORMALDEHYDE AND NITRILES OR AMIDES

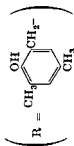


	Product from Formaldehyde	Position(s) of Substituent(s)	Method	References (Yield, %)
HCN and <i>m</i> -Xylene		4.	H ₂ SO ₄ , CH ₃ CO ₂ H, 90°	5 (25)
CH ₃ CN and Benzene		1.	H ₂ SO ₄ , CH ₃ CO ₂ H, 90°	5 (50)
Bromobenzene		4.	Concl., H ₂ SO ₄	5 (37)
Anisole		4.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (28)
Toluene		2. (10 %) and 4. (36 %)	H ₂ SO ₄ , CH ₃ CO ₂ H, 90°	5 (53)
Ethylbenzene		4.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (19)
Cumene		4.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (75)
<i>o</i> -Xylene		2.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (54)
<i>m</i> -Xylene		4.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (52)
		4,6.	85 % H ₃ PO ₄ , 90°	5 (66)
		4,6.	H ₂ SO ₄ , CH ₃ CO ₂ H, 90°	5 (75)
		2. (21 %) and 2,5. (55 %)	H ₂ SO ₄ , CH ₃ CO ₂ H, 90°	5 (89)
<i>p</i> -Xylene		5.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (67)
1,2,4-Trimethylbenzene		5.	H ₂ SO ₄ , CH ₃ CO ₂ H, 90°	5 (45)
N-(2,4-Dimethylbenzyl)acetamide		3,6.	H ₂ SO ₄ , CH ₃ CO ₂ H, 85°	5 (72)
1,2,4,5-Tetramethylbenzene (durene)		1. (12 %), 1,4. (25 %) and 1,5(7). (6 %)	H ₂ SO ₄ , CH ₃ CO ₂ H, 90°	5 (>43)
Naphthalene				
CH ₃ CN and <i>m</i> -Xylene		4,6.	H ₂ SO ₄ , CH ₃ CO ₂ H	5
CH ₃ CH ₂ CN and <i>m</i> -Xylene		4,6.	H ₂ SO ₄ , CH ₃ CO ₂ H	5

$CH_3=CHCN$ and Toluene	4.	H_2SO_4, CH_3CO_2H	5 (89)
Cumene	4.	H_2SO_4, CH_3CO_2H	5 (53)
<i>m</i> -Xylene	4,6.	85% $H_3PO_4, 80^\circ$	5
C_6H_5CN and <i>m</i> -Xylene	4,6.	H_2SO_4, CH_3CO_2H	5
2-Pyrrolidinone and 4-Nitrotoluene	2.	Concd. H_2SO_4	34 (37)
γ -Valerolactam and 4-Nitro-1,3-xylene	6.	Concd. H_2SO_4	34 (41)
Succinimide and 4-Nitrotoluene	2.	Concd. H_2SO_4	34 (81)
Copper phthalocyanine	x .	95% $H_2SO_4, 75^\circ$	50
4-Cyclohexene-1,2-dicarboximide and 4-Chloronitrobenzene	3.	Concd. H_2SO_4	34 (75)
Phthalimide and Copper phthalocyanine	x to x, x, x, x .	H_2SO_4 , oleum, or P_2O_5	50
Urea and 2,4-Nylenol		H_2NCONR_2 and $HNHCONH_2$	59
		$HCO_2H, 50^\circ$	
		$\left(R = \begin{array}{c} CH_2 \\ \\ \text{C}_6H_3(OH)(CH_2-) \\ \\ CH_2 \end{array} \right)$	
Sulfanilamide and 4-Methyl-2-thioureacl	5.	HCl, CH_3CO_2H , heat	60
N ⁺ -Acetyl sulfanilamide and 4-Methyl-2-thioureacl	5.	HCl, CH_3CO_2H , heat	60

Note: References 382 to 537 are on pp. 266-269.

CH ₂ =CHCN and Toluene	4.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (89)
Cumene	4.	H ₂ SO ₄ , CH ₃ CO ₂ H	5 (53)
m-Xylene	4,6.	85% H ₃ PO ₄ , 90°	5
C ₆ H ₅ CN and m-Xylene	4,6.	H ₂ SO ₄ , CH ₃ CO ₂ H	5
2-Pyrrolidinone and 4-Nitrotoluene	2.	Concd. H ₂ SO ₄	34 (37)
γ-Valerolactam and 4-Nitro-1,3-xylene	6.	Concd. H ₂ SO ₄	34 (41)
Succinimide and 4-Nitrotoluene	2.	Concd. H ₂ SO ₄	34 (81)
Copper phthalocyanine	x.	95% H ₂ SO ₄ , 75°	50
4-Cyclohexene-1,2-dicarboximide and 4-Chloronitrobenzene	3.	Concd. H ₂ SO ₄	34 (75)
Phthalimide and Copper phthalocyanine	x. to x,x,x,x.	H ₂ SO ₄ , oleum, or P ₂ O ₅	50
Urea and 2,4-Xylenol	H ₂ NCONR ₂ and RNHCONR ₂	HCO ₂ H, 50°	59
Sulfanilamide and 4-Methyl-2-thiouracil	5.	HCl, CH ₃ CO ₂ H, heat	60
N ⁴ -Acetyl sulfanilamide and 4-Methyl-2-thiouracil	5.	HCl, CH ₃ CO ₂ H, heat	60



Note: References 382 to 537 are on pp. 260-269.

TABLE V
ASYMMETRYLATION OF AROMATIC CARBON ATOMS WITH ETHERS OF N-METHYLOL-AMIDES AND -IMIDES

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$[(CH_3)_2CHCH_2CONHCH_2]_2O$ and 2,4-Xylenol	6-	H_2SO_4, C_2H_5OH	54
$o-C_6H_4(CO)_2NCH_2OCH_3$ and Copper phthalocyanine	3,3'-	100 % $H_2SO_4, 100^\circ$	64
$o-C_6H_4(CO)_2NCH_2OC_2H_5$ and Benzene	1-	100 % $H_2SO_4, 90^\circ$, 1.5 hr.	63 (5)
Nitrobenzene	3-	100 % $H_2SO_4, 80^\circ$, 1.5 hr.	63 (41)
$[o-C_6H_4(CO)_2NCH_2]_2O$ and Phenol	3,3' and 3,3'-	Concd. H_2SO_4	61
4-Nitrophenol	2-	Concd. H_2SO_4	61
2-Nitrotoluene	5(?)	Concd. H_2SO_4	61
Copper phthalocyanine	3-	100 % $H_2SO_4, 75^\circ$	50
$(HOCH_2NHCONHCH_2)_2O$ and 2,4-Xylenol	$RNHCONR_2$, (RNH) $_2CO$, and $RNHCONH_2$	$HCl, C_2H_5OH, 50^\circ$	62
$(C_6H_5NHCONHCH_2)_2O$ and 2,4-Xylenol	$\left(R = \begin{array}{c} OH \\ \\ \text{C}_6H_3(CH_3)_2CH_2- \end{array} \right)$	$HCO_2H, 50^\circ$	54
$(C_6H_5NHCONHCH_2)_2O$ and 2,4-Xylenol	6-	$HCO_2H, 50^\circ$	54 (90)

Note: References 382 to 537 are on pp. 266-269.

TABLE VI
AMIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-HALOMETHYL-AMIDES,
-IMIDES, AND -CARBAMYL COMPOUNDS
 $\text{RCON(R')CH}_2\text{X} + \text{ArH} \rightarrow \text{RCON(R')CH}_2\text{Ar}$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$\text{CH}_3\text{CON}(\text{CH}_3)\text{CH}_2\text{Cl}$ and Benzene	1-	$\text{AlCl}_3, \text{C}_6\text{H}_6$	32
4-Chlorophenol	2-	AlCl_3	32
Anisole	4-	AlCl_3	32
Toluene	4-	$\text{AlCl}_3, \text{C}_6\text{H}_5\text{CH}_3$	32 (92)
$\text{CH}_3\text{CON}(\text{C}_3\text{H}_7, n)\text{CH}_2\text{Cl}$ and Benzene	1-	$\text{AlCl}_3, \text{C}_6\text{H}_6$	32
$\text{CH}_3\text{CON}(\text{CH}_2\text{C}_6\text{H}_5)\text{CH}_2\text{Cl}$ and Toluene	4-	$\text{AlCl}_3, \text{C}_6\text{H}_5\text{CH}_3$	32
$n\text{-C}_{17}\text{H}_{35}\text{CON}(\text{CH}_3)\text{CH}_2\text{Cl}$ and Phenol			
$\text{C}_6\text{H}_5\text{CON}(\text{CH}_3)\text{CH}_2\text{Cl}$ and Toluene	4-	$\text{CH}_3\text{CO}_2\text{H}, 20-60^\circ$	67
1,4-Dichloromethylpiperazine-2,5-dione* and Benzene		$\text{AlCl}_3, \text{C}_6\text{H}_5\text{CH}_3$	32
Naphthalene	1-	$\text{AlCl}_3, \text{CS}_2$	65 (43)
2-Naphthol	x-	No solvent, 150°	65 (64)
	1-	$\text{C}_6\text{H}_6, 80^\circ$	65 (89)
N-Chloromethylsuccinimide and Benzene	1-	$\text{AlCl}_3, \text{CS}_2$	68

Note: References 382 to 537 are on pp. 266-269.

* Bifunctional reaction.

TABLE VI—Continued
 ARIDOMETHYLATION OF AROMATIC CARBON ATOMS WITH N-HALOMETHYL-AMIDES,
 -IMIDES, AND -CARBAMYL COMPOUNDS
 $RCON(R')CH_2X + ArH \rightarrow RCON(R')CH_2Ar$

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
N-Chloromethylmaleimide and Benzene	1-	ZnCl ₂ , 80°	8 (83)
Phenol	2,4-	ZnCl ₂ , C ₆ H ₆ , 80°	8 (40)
<i>o</i> -C ₆ H ₄ (CO) ₂ NCH ₂ Cl and Benzene	1-	ZnCl ₂ , C ₆ H ₆	68
Phenol	2- and 4-	ZnCl ₂ , C ₆ H ₆	68
Anisole	4-	ZnCl ₂ , 120°	68 (100)
	2- and 4-	ZnCl ₂ , 130°	378 (65)
	4-	ZnCl ₂ , 150°	407
<i>n</i> -C ₃ H ₇ OC ₆ H ₅	2-	ZnCl ₂ , 90–130°	69 (70)
4-Chlorophenol	4-	No catalyst, 120°	68
Guinacol	4-	ZnCl ₂ , 120°	68
2-Nitrotoluene	4-	ZnCl ₂ , 100°	68
<i>m</i> -Xylene	5-	ZnCl ₂ , C ₆ H ₅ NO ₂ , 100°	68
N-(2,4-Dimethylbenzyl)phthalimide	1-	ZnCl ₂ , molten	68
Naphthalene	4,8(?)	ZnCl ₂ , C ₆ H ₅ NO ₂ , 120°	68
N-(1-Naphthylmethyl)phthalimide	4-	AlCl ₃ , C ₆ H ₅ Cl ₃ , 110°	379 (97)
1-Naphthol-8-sulfonic acid γ-sultone	9,10-	ZnCl ₂ , C ₆ H ₅ NO ₂ , 100°	68
Anthracene	3(?)	ZnCl ₂ , C ₆ H ₅ NO ₂ , 140°	408, 409
7H-Benz [de] anthracen-7-ono (benzanthrone)	5a-	AlCl ₃ , piperidine, 140°	64
Copper phthalocyanine	3,3a-	100% H ₂ SO ₄ , 80°	64
	6a-	AlCl ₃ , pyridine, 130°	64
Copper tetraphenylphthalocyanine	4a-	Concd. H ₂ SO ₄	64

$\alpha\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{Br}$ and

Benzene

Phenol

- 1-
2- and 4-
2(f)-
4-
x-
4-
x-

Thymol

Phenylacetic acid

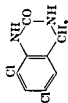
2-Naphthol

$\text{ClCONHCH}_2\text{Cl}$ and

Phenol



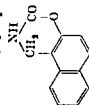
2,4-Dichloroaniline



m-Xylene

β -Naphthol

2,4-(CH_2) $_2\text{C}_6\text{H}_3\text{CH}_2\text{NCO}$



ZnCl_2 , 80°
 C_6H_6 , no catalyst, 80°
Heat, no solvent
Heat
Heat
 ZnCl_2 , 120°
Heat
Pentane, 40°, 3 hr.

73 (5)

Heptane, 25°, 16 hr.

73 (55)

ZnCl_2 , CH_2Cl_2 , 58°
Pentane, 25°, 24 hr.

73 (35)

73 (25)

Note References 392 to 337 are on pp. 266-269.

TABLE VII
 α -AMIDOALKYLATION OF AROMATIC CARBON ATOMS WITH
 N,N'-METHYLENE-, -ARYLEIDENE-, AND -ARYLEIDENE-BISAMIDES
 $(\text{RCONH})_2\text{CH}_2 + \text{ArH} \rightarrow \text{RCONHCH(R')Ar} + \text{RCONH}_2$
 (R' = H, alkyl, or aryl)

Product Derived from	Position(s) of Substituent(s)	Method	References (Yield, %)
$(\text{HCONH})_2\text{CH}_2$ and 2,4-Xylenol	6-	POCl_3 , 95°, 1 hr.	75 (38)
$(\text{CH}_3\text{CONH})_2\text{CH}_2$ and Phenol	2- (25 %) and 4- (21 %)	POCl_3 , CHCl_3 , 65°, 4 hr.	76, 77 (>46)
4-Nitrophenol	2-	POCl_3 , 95°, 1 hr.	18 (85)
Anisole	4- (46 %) and <i>o,o'</i> - (26 %)	POCl_3 , 95°, 3 hr.	77 (72)
4-Methoxytoluene	3-	POCl_3 , 95°, 1 hr.	18 (93)
2-Methylacetanilide	4-	POCl_3 , 130°, 1 hr.	18 (86)
4-Methylacetanilide	2-	POCl_3 , 130°, 1 hr.	18 (71)
2,4-Xylenol	6-	POCl_3 , 95°, 1 hr.	75 (94)
Salicylic acid	5-	POCl_3 , 95°, 1 hr.	76, 78 (>30)
2-Naphthol	1-	POCl_3 , CHCl_3 , 65°	18 (94)
8-Hydroxyquinoline	5-	POCl_3 , 95°, 1 hr.	18 (84)
$(\text{CH}_3\text{CH}_2\text{CONH})_2\text{CH}_2$ and 2,4-Xylenol	6-	POCl_3 , 95°, 1 hr.	75 (89)
$(\text{C}_6\text{H}_5\text{CONH})_2\text{CH}_2$ and Benzene	1-	100 % H_2SO_4 , 95°, 6 hr.	63 (63)
2,4-Xylenol	6-	POCl_3 , 95°, 1 hr.	75 (93)
ω -C ₆ H ₄ (CO) ₂ NCH ₂ NHCO ₂ C ₆ H ₅ and Benzene	1-	100 % H_2SO_4 , 90°, 5.5 hr.	63 (24)*

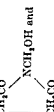
(C ₆ H ₅ NHCONH) ₂ CH ₃ and 2,4-Xylenol	6.	HCO ₂ H, 50°	55
(p-CH ₃ C ₆ H ₄ NHCONH) ₂ CH ₃ and 2,4-Xylenol	6.	HCO ₂ H, 50°	55
(CH ₃ CONH) ₂ CHCH ₃ and p-Cresol	2.	POCl ₃ , C ₆ H ₆ , 80°	18 (93)
2,4-Xylenol	6.	POCl ₃ , C ₆ H ₆ , 80°	75 (74)
2-Naphthol	1.	POCl ₃ , CHCl ₃ , 65°	18 (91)
(CH ₃ CONH) ₂ CHC ₆ H ₅ and Phenol	2.	190°, 4 hr.	74 (41)
Phenyl acetate	2.	190°, 4 hr.	74 (43)
4-Nitrophenol	2.	POCl ₃ , 95°, 1 hr.	18 (81)
p-Cresol	2.	190°, 4 hr.	74 (49)
4-Methoxytoluene	3.	POCl ₃ , 95°, 1 hr.	18 (91)
2-Methylacetanilide	4.	POCl ₃ , 130°, 2 hr.	18 (98)
4-Methylacetanilide		POCl ₃	76
2,4-Xylenol	6.	POCl ₃ , 95°, 1.5 hr.	75 (98)
2,6-Xylenol	6.	190°, 4 hr.	74 (74)
2-Naphthol	4.	190°, 4 hr.	74 (30)
(C ₆ H ₅ CONH) ₂ CHC ₆ H ₅ and Phenol	1.	POCl ₃ , C ₆ H ₆ , 80°, 1.5 hr.	18 (98)
Phenyl benzoate	2.	190°, 4 hr.	74 (93)
2-Naphthol	1.	190°, 4 hr.	74 (69)
		190°, 4 hr.	74 (12)
			74 (93)

Note. References 342 to 337 are on pp. 266-269.

* The only product obtained was N-benzylphthalimide.

TABLE VIII
 α -AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
 N-MONOMETHYLOL AND N- α -ALKYLOL DERIVATIVES OF AMIDES,
 IMIDES, AND CARBAMYL COMPOUNDS

Product Derived from	Method	References (Yield, %)
HCONHCH ₃ OH and Trinitromethane	H ₂ O	88
CH ₃ CONHCH ₃ OH and Trinitromethane	H ₂ O, pH 7, 70°, 10 min.	88 (75)
CH ₃ ClCONHCH ₃ OH and Cyclohexane-1,3-dione	H ₂ SO ₄ , 3 days	85 (0)
(O ₂ N) ₂ CCH ₂ CH ₂ CONHCH ₃ OH and Trinitromethane	CH ₃ OH, 12 hr.	87 (80)
CH ₃ -CHCONHCH ₃ OH and Trinitromethane	H ₂ O, 5°, 48 hr.	87 (5)
CH ₃ -C(CH ₃)CONHCH ₃ OH and Trinitromethane	C ₂ H ₅ OH, CH(NO ₂) ₃ (2 equiv.), 12 hr.	87 (88)*
C ₆ H ₅ CONHCH ₃ OH and Trinitromethane	H ₂ O, 1 day	87 (87)
Cyclohexane-1,3-dione	H ₂ O, 80°	88
5,5-Dimethylcyclohexane-1,3-dione	Concd. H ₂ SO ₄ , 3 days	85 (36)
1-Phenylbutane-1,3-dione	C ₂ H ₅ OH, concd. HCl, 3 days	85 (20)
1,3-Diphenylpropane-1,3-dione	CH ₃ CO ₂ H, ZnCl ₂ , 3 days	85 (40)
	CH ₃ CO ₂ H, BF ₃ -etherate, 20 hr.	85 (65)
	H ₂ SO ₄ , 25°, 3 days	85†
	C ₂ H ₅ OH	86
	Concd. H ₂ SO ₄ , 40 hr.	86
x-O ₂ NC ₆ H ₄ CONHCH ₃ OH and Trinitromethane	CH ₃ CO ₂ H, BF ₃ -etherate, 20 hr.	85 (74)
	H ₂ O	88

o-C ₆ H ₄ (CO) ₂ NCH ₂ OH and Pentane-2,4-dione	Concd. H ₂ SO ₄ , 0°, 1 day	85 (85)
5,5-Dimethylcyclohexane-1,3-dione	H ₂ SO ₄ , 1 day	85 (74)
1-Phenylbutane-1,3-dione	Concd. H ₂ SO ₄ , 1 day	85 (83)
1,3-Diphenylpropane-1,3-dione	Concd. H ₂ SO ₄ , 1 day	85 (84)
Ethyl acetoacetate	Concd. H ₂ SO ₄ , cold, 1 day	85†
Malonic acid	H ₂ SO ₄ , standing overnight	84 (0)
Diethyl malonate	H ₂ SO ₄ , 2 days	85 (0)
1,2-Diphenylpyrazolidine-3,5-dione	H ₂ SO ₄ , 3 days	84 (0)
CH ₂ CO  and CH ₂ CO	Concd. H ₂ SO ₄ , 1 day	85 (83)
Cyclohexane-1,3-dione	H ₂ SO ₄ , 3 days	85 (0)
C ₆ H ₅ O ₂ CNHCH ₂ OH and Trinitromethane	H ₂ O, 80°, short reaction time	88 (90)
CH ₂ NHCONHCH ₂ OH and Trinitromethane	H ₂ O	88
Acetone	H ₂ O, NaHCO ₃ , 5 hr.	89 (0)
Pentane-2,4-dione	H ₂ O, K ₂ CO ₃ , 1 day	89 (75)
Ethyl acetoacetate	H ₂ O, K ₂ CO ₃ , 20 hr.	89 (80)
Diethyl malonate	No solvent, 100°, 4 hr	89 (90)
Ethyl cyanoacetate		89 (90)

Note References 382 to 537 are on pp. 266-269.

* Trinitromethane added to the carbon-carbon double bond during the amidoalkylation. The product was the saturated material (O₂N)₃CC₆H₄CH₂CONHCH₂C(NO₂)₃.

† The product was not characterized.

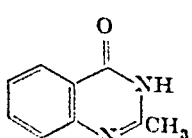
‡ Mono- (33%) and bis- (16%) amidoalkylation occurred with concomitant decarboxylation.

TABLE IX
AMIDOMETHYLATION OF ALIPHATIC CARBON ATOMS WITH
DIMETHYLOL DERIVATIVES OF FUMARAMIDE AND OF UREA

Product Derived from	Method	References (Yield, %)
HOCH ₂ NHCOCH HCCONHCH ₂ OH and Trinitromethane	H ₂ O, pH 0.8, 90 min.	87 (48)
CO(NHCH ₂ OH) ₂ and Trinitromethane	H ₂ O, 40°, 5 min. Urea, formalin (2 equiv.), 22 hr.	88 (77) 88 (88)
Acetylene	10 atm., 40°, 10-20 hr.	90

Note: References 382 to 537 are on pp. 266-269.

TABLE X
α-AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
FORMALDEHYDE OR ACETALDEHYDE AND SULFONAMIDES

Product Derived from	Method	References
CH ₃ (CH ₂) ₂ CH ₂ SO ₂ NH ₂ , CH ₂ O, and Potassium cyanide	Aq. CH ₂ O, 80°, 1 hr.	91
CH ₃ (CH ₂) ₆ CH ₂ SO ₂ NH ₂ , CH ₂ O, and Potassium cyanide	Aq. CH ₂ O, 45°, 2 hr.	91
C ₆ H ₅ SO ₂ NH ₂ and HOCH ₂ CN	8 % NaOH, 90°, 1 hr.	91
C ₆ H ₅ SO ₂ NH ₂ , CH ₂ O, and Sodium cyanide	Aq. CH ₂ O, 70°, 2 hr.	91
C ₆ H ₅ SO ₂ NH ₂ , CH ₃ CHO, and Potassium cyanide	H ₂ O, 95°, 2 hr.	91
p-H ₂ NC ₆ H ₄ SO ₂ NH ₂ , (CH ₂ O) _x , and 2-Picoline	Paraffin oil, 130°	92
Quinaldine	Paraffin oil, 130°	92
9-Methylacridine	Paraffin oil, 180°	92
9-Ethylacridine	Paraffin oil, 130°	92
	No solvent, 160-170°	92
p-CH ₃ CONHC ₆ H ₄ SO ₂ NH ₂ , (CH ₂ O) _x , and 2-Picoline	Paraffin oil, 200°	92
p-CH ₃ C ₆ H ₄ SO ₂ NH ₂ , CH ₂ O, and Sodium cyanide	H ₂ O, 70°, 2 hr.	91

Note: References 382 to 537 are on pp. 266-269.

TABLE XI
 α -AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
 ETHERS AND ESTERS OF N-METHYLOL- AND N- α -ALKYLOL-AMIDE
 DERIVATIVES

Product Derived from	Method*	References (Yield, %)
$(C_2H_5O_2CNHCHCl)_2O$ and Diethyl malonate	KOC_2H_5 , ether, 0°	94 (35), 95
$C_2H_5O_2CNHCH(OCOCH_3)CCl_3$ and Potassium cyanide	H_2O , 0° , 3-4 hr.	94 (53)†
$CH_2=CHCONHCH_2OCOC_2H_5$ and Trinitromethane	$(CH_2Cl)_2$, 1 equiv., reflux, 0.5 hr. CH_3NO_2 , 2 equiv., 101° , 15 min. CH_3NO_2 , 101° , 0.5 hr. $(CH_2Cl)_2$, 2 equiv., 83° , 0.5 hr. C_2H_5OH , 2 equiv., 78° , 0.5 hr. H_2O , 2 equiv., 25° , 4 hr.	93 (4)‡ 93 (49)‡ 93 (12)‡ 93 (43)‡ 93 (55)‡ 93 (10)‡
$CH_2=C(CH_3)CONHCH_2OCOC_2H_5$ and Trinitromethane	$(CH_2Cl)_2$, 25° , 12 hr. H_2O , 25° , 0.5 hr. $(CH_2Cl)_2$, 2 equiv., 25° , 3 hr.	93 (50) 93 (64) 93 (65)
$CH_3CO_2CH_2NHCOCH$ HCCONHCH ₂ OCOC ₂ H ₅ and Trinitromethane	H_2O , reflux, 25 min.	93 (2)
$C_2H_5CO_2CH_2NHCOCH$ HCCONHCH ₂ OCOC ₂ H ₅ and Trinitromethane	CH_3NO_2 , reflux, 4 hr.	93 (47)

Note: References 392 to 537 are on pp. 266-269

* The abbreviation "equiv." refers to the number of equivalents of trinitromethane

† The product obtained was of the type $C_2H_5O_2CNH(CN)-CCl_3$

‡ Trinitromethane added to the carbon-carbon double bond during amidoalkylation. The product was the saturated material $(O_2N)_3CCH_2CH_2(CNHCH_2(CNO_2))_2$

TABLE XII

α -AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
N-HALOMETHYL AND N- α -HALOALKYL DERIVATIVES OF
AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

Product Derived from	Method*	References (Yield, %)
HCONHCH ₂ Cl and Diethyl methylmalonate	Dioxane	96, 100 (20)
HCONHCHClCCl ₃ and Diethyl malonate	(C ₂ H ₅) ₂ O, reflux, 3-4 hr.	160
CH ₃ CONHCH ₂ Cl and Diethyl malonate	Dioxane, 50°, 1 hr.	96, 100 (25)
Diethyl methylmalonate	Dioxane, 70°, 1.5 hr.	100 (31)
Ethyl cyanoacetate	Dioxane, 70°, 1 hr.	96, 100 (27)
CH ₃ CON(CH ₃)CH ₂ Cl and Diethyl methylmalonate	Dioxane, 40°, 30 min.	98 (68)
CH ₃ CON(C ₃ H ₇ -n)CH ₂ Cl and Diethyl methylmalonate	Dioxane, 100°, 1 hr.	98 (38)
CH ₃ CON(C ₃ H ₇ -i)CH ₂ Cl and Diethyl methylmalonate		98 (28)
CH ₃ ClCONHCH ₂ Cl and Diethyl methylmalonate	Dioxane	96
CCl ₃ CONHCH ₂ Cl and 1-Phenylbutane-1,3-dione	Dioxane	96 (51)
Diethyl ethylmalonate	(C ₂ H ₅) ₂ O, reflux, 15 min.	100 (62)
α -Phenylacetoacetonitrile	Dioxane	96 (57)
1-Chloromethyl-2-pyrrolidinone and Diethyl methylmalonate	Dioxane-acetonitrile, 40°, 2 hr.	33 (40)
N-Chloromethyl- ϵ -caprolactam and Diethyl methylmalonate	Dioxane, 100°, 0.5 hr.	33 (40)
C ₆ H ₅ CONHCH ₂ Cl and Pentane-2,4-dione	(C ₂ H ₅) ₂ O	96 (60)†
3-Methylpentane-2,4-dione	(C ₂ H ₅) ₂ O, reflux, 2 hr.	410 (88)
Ethyl acetoacetate	(C ₂ H ₅) ₂ O, reflux, 0.5 hr.	96, 100 (57)
Ethyl α -methylacetoacetate	(C ₂ H ₅) ₂ O, reflux, 0.5 hr.	96, 100 (50)
Ethyl α -isopropylacetoacetate	(C ₂ H ₅) ₂ O, reflux, 0.5 hr.	96, 100 (50)
2-Carboethoxycyclohexanone	Dioxane, 100°, 3 hr.	96 (84)
Dimethyl malonate	(C ₂ H ₅) ₂ O	96 (81)†
Diethyl methylmalonate	(C ₂ H ₅) ₂ O, reflux, 1 hr.	96, 100 (77)
Diethyl ethylmalonate	(C ₂ H ₅) ₂ O, reflux, 0.5 hr.	96 (72), 100 (72)
Ethyl α -cyanopropionate	(C ₂ H ₅) ₂ O, reflux, 1 hr.	96 (48), 100 (48)
1-Phenylbutane-1,3-dione	(C ₂ H ₅) ₂ O, reflux, 0.5 hr.	96 (51), 100
α -Phenylacetoacetonitrile	(C ₂ H ₅) ₂ O, reflux, 1.5 hr.	96 (79), 100 (51)
C ₆ H ₅ CON(CH ₃)CH ₂ Cl and Ethyl methylacetoacetate	Dioxane, 100°, 1 hr.	98 (28)
Diethyl methylmalonate	Dioxane, 100°, 1 hr.	98 (37)
C ₆ H ₅ CONHCHClCCl ₃ and 1-Phenylbutane-1,3-dione	Dioxane, 50°, 3 hr.	101 (73)

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise noted, the sodium salt of the active methylene compound was prepared before the alkylating agent was added.

† The bisamidoalkylated product was obtained.

TABLE XII—Continued

α -AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
N-HALOMETHYL AND N- α -HALOALKYL DERIVATIVES OF
AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

Product Derived from	Method*	References (Yield, %)
2,4 Cl ₂ C ₆ H ₃ CONHCH ₂ Cl and Diethyl methylmalonate	Dioxane	96
2-CH ₃ O-5 ClC ₆ H ₃ CONHCHClCCl ₃ and Potassium cyanide	CH ₃ COCH ₃ , 0.5 hr.	107 (ca 39)‡
2-CH ₃ O-3,5 Cl ₂ C ₆ H ₃ CONHCHClCCl ₃ and Potassium cyanide	CH ₃ COCH ₃ , 0.5 hr.	107 (ca 39)‡
2-CH ₃ O-5-BrC ₆ H ₃ CONHCHClCCl ₃ and Potassium cyanide	CH ₃ COCH ₃ , 0.5 hr.	107 (ca 39)‡
2-CH ₃ O-3,5-Br ₂ C ₆ H ₃ CONHCHClCCl ₃ and Potassium cyanide	CH ₃ COCH ₃ , 0.5 hr.	107 (ca 39)‡
m-CH ₃ C ₆ H ₄ CONHCHClCCl ₃ and Potassium cyanide	CH ₃ COCH ₃ , 0.5 hr.	106‡
p-CH ₃ C ₆ H ₄ CONHCHClCCl ₃ and Potassium cyanide	CH ₃ COCH ₃ , 0.5 hr.	106‡
o C ₆ H ₄ (CO) ₂ NCH ₂ Cl and Diphenylacetaldehyde	(C ₆ H ₅) ₂ O	97
2-Methyl-1-phenylbutane-1,3 dione	CH ₃ COCH ₃ , reflux, 30 min	97 (54)
Cyclohexane-1,3-dione	CH ₃ OH/C ₆ H ₆ , reflux	85 (20)
1,1,4-Trimethyleyclohexane-3,5- dione	C ₆ H ₅ OH, reflux, 30 min.	97 (36)
Ethyl α methylacetoacetate	(C ₆ H ₅) ₂ O	97 (63)
Diethyl methylmalonate	Dioxane	97 (47)
	(C ₆ H ₅) ₂ O	97 (81)
Diethyl ethylmalonate	(C ₆ H ₅) ₂ O	97 (67)
Diethyl acetamidomalonate	C ₆ H ₅ OH	97 (60)
Diethyl phenylmalonate	(C ₆ H ₅) ₂ O	97 (83)
α -Phenylacetoacetoneitrile	C ₆ H ₅ OH/CH ₃ COCH ₃ , reflux 30 min	97 (72)
o C ₆ H ₄ (CO) ₂ NCH ₂ Br and 3-Phenyl-2-benzofuranone	(C ₆ H ₅) ₂ O, reflux, 2-3 hr	105 (73)
Ethyl acetoacetate	C ₆ H ₅ OH	104 (0)
Ethyl 4,4-diethoxyacetoacetate	C ₆ H ₅ OH, reflux, 3 hr	104 (0)
Diethyl malonate	C ₆ H ₆	102 (0)
Potassium cyanide	CH ₃ COCH ₃ , reflux, 3 hr	104 (0)
N-Chloromethylsaccharin and Ethyl methylacetoacetate	(C ₆ H ₅) ₂ O, reflux, 3 hr	99 (56)
Diethyl methylmalonate	(C ₆ H ₅) ₂ O, reflux, 4 hr	99 (59)
Ethyl methylcycanoacetate	(C ₆ H ₅) ₂ O, reflux, 2 hr	99 (61)
C ₆ H ₅ O ₂ CNHCCHClCCl ₃ and Ethyl acetoacetate	(C ₆ H ₅) ₂ O, reflux, 6-7 hr	160

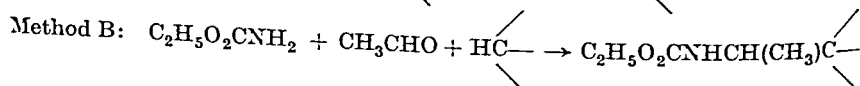
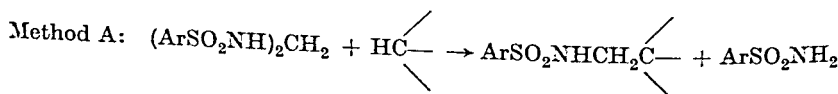
Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise noted, the sodium salt of the active methylene compound was prepared before the alkylating agent was added.

‡ The product was of the type ArCNHC(CN)–CH₂

TABLE XIII

α -AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
 N,N'-METHYLENEDISULFONAMIDES AND N,N'-ETHYLIDENE-
 BISURETHAN OR THEIR PRECURSORS

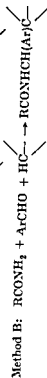
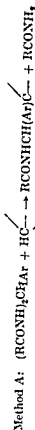


Product Derived from	Method	References (Yield, %)
$(\text{C}_6\text{H}_5\text{SO}_2\text{NH})_2\text{CH}_2$ and Cyclohexane-1,3-dione	A; H_2SO_4 , 25° , 2 days	85 (18)
$(p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH})_2\text{CH}_2$ and Cyclohexane-1,3-dione	A; H_2SO_4 , 25° , 2 days	85 (19)
$\text{C}_2\text{H}_5\text{O}_2\text{CNH}_2$, CH_3CHO , and Pentane-2,4-dione	B; $\text{C}_2\text{H}_5\text{OH}$, HCl , 24 hr.	108 (30)

Note: References 382 to 537 are on pp. 266-269.

TABLE XIV

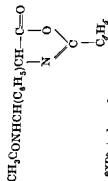
α-AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
N,N'-ARYLDIENEISANIDES OR THEIR PRECURSORS



Product Derived from	Method	References (Yield, %)
Acetamide, benzaldehyde, and Nitromethane	A; $(CH_3CO)_2O$, 100°, 24 hr.	113 (32)
Cyclohexane-1,3-dione	A; $(CH_3CO)_2O$, 130°, 3 hr.	85 (9)
5,5-Dimethylcyclohexane-1,3-dione	A; $(CH_3CO)_2O$, 130°, 3 hr.	85 (12)
Ethyl nitroacetate	A; $(CH_3CO)_2O$, 100°, 7 hr.	112 (85)
Ethyl acetoacetate	B; $(CH_3CO)_2O$, 100°, 7 hr.	112 (91)
Dimethyl malonate	A; $(CH_3CO)_2O$, 120°, 5 hr.	114 (72)
Diethyl malonate	A; $(CH_3CO)_2O$, HCl, 155°, 3 hr.	85 (62)
Diethyl ethylmalonate	A; $(CH_3CO)_2O$, 155°, 3 hr.	115 (62)
Hippuric acid	A; 180°, 9 hr.	115 (11)
	A; $(CH_3CO)_2O$, 155°, 5 hr.	115 (76)
	A; CH_3CO_2H , $(CH_3CO)_2O$, 110°	117 (61)*

Note: References 382 to 537 are on pp. 266-269.

* The product was



All other alkylations of hippuric acid gave the expected products.

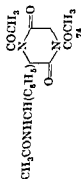
TABLE XIV—Continued
 α -AMINOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
 N,N'-ARYLDIENEISAMIDES OR THEIR PRECURSORS

Method A: $(RCONH)_2CHAr + HC \begin{array}{c} \diagup \\ \diagdown \end{array} \rightarrow RCONHCH(Ar)C \begin{array}{c} \diagup \\ \diagdown \end{array} + RCONH_2$	Method B: $RCONH_2 + ArCHO + HC \begin{array}{c} \diagup \\ \diagdown \end{array} \rightarrow RCONHCH(Ar)C \begin{array}{c} \diagup \\ \diagdown \end{array}$	References (Yield, %)
Product Derived from	Method	
Acetanilide, benzaldehyde (<i>contd.</i>) and $\begin{array}{c} CH_3CHCO \\ \quad \diagup \\ NH \\ \quad \diagdown \\ S \cdot CS \end{array}$	A: $(CH_3CO)_2O$, 150°, 2 hr.	411 (93)
Piperazine-2,5-dione	A: $(CH_3CO)_2O$, 165°, 12 hr.	100 (29) [†]
Acetanilide, o-nitrobenzaldehyde, and Ethyl nitroacetate	B: $(CH_3CO)_2O$, 100°, 7 hr. A: CH_3CO_2H , $(CH_3CO)_2O$	112 (12) 117 (0)
Hippuric acid	A: CH_3CO_2H , $(CH_3CO)_2O$	117 (0)
Acetanilide, p-nitrobenzaldehyde, and Hippuric acid	A: CH_3CO_2H , $(CH_3CO)_2O$, 1 hr.	117 (57) [‡]
Acetanilide, o-methoxybenzaldehyde, and Hippuric acid	A: $(CH_3CO)_2O$, 155°, 3 hr.	115 (45)
Acetanilide, p-methoxybenzaldehyde, and Diethyl malonate	A: CH_3CO_2H , $(CH_3CO)_2O$, 1 hr.	117 (60) [‡]
Hippuric acid	A: $(CH_3CO)_2O$, 100°, 7 hr.	112 (44)
Acetanilide, veratraldehyde, and Ethyl nitroacetate	B: $(CH_3CO)_2O$, 100°, 7 hr. A: $(CH_3CO)_2O$, 120°, 6 hr.	112 (41) 114 (75)

Acetamide, piperonal, and Ethyl nitroacetate	B; (CH ₃ CO) ₂ O, 100°, 8.5 hr.	112 (49)
Ethyl acetoacetate	A; (CH ₃ CO) ₂ O, 120°, 5 hr.	114 (50)
Diethyl malonate	A; (CH ₃ CO) ₂ O, 155°, 3 hr.	115 (53)
Hippuric acid	A; CH ₃ CO ₂ H, (CH ₃ CO) ₂ O, heat, 1.5 hr.	117 (50)†
Acetamide, O-acetylvanillin, and Ethyl nitroacetate	A; (CH ₃ CO) ₂ O, 100°, 7 hr.	112 (43)
Acetamide, p-tolualdehyde, and Hippuric acid	B; (CH ₃ CO) ₂ O, 100°, 7 hr.	112 (10)
Benzamide, benzaldehyde, and Cyclohexane-1,3-dione	A; CH ₃ CO ₂ H, (CH ₃ CO) ₂ O, heat, 1.5 hr.	117 (55)†
5,5-Dimethylcyclohexane-1,3-dione	A; (CH ₃ CO) ₂ O, 140°, 4 hr.	85 (40)
Ethyl nitroacetate	A; (CH ₃ CO) ₂ O, 130°, 3 hr.	85 (0)
Dimethyl malonate	A; (CH ₃ CO) ₂ O, 135°, 2 hr.	85 (47)
Benzamide, o-nitrobenzaldehyde, and Cyclohexane-1,3-dione	A; (CH ₃ CO) ₂ O, 155°, 3 hr.	85 (52)
	A; (CH ₃ CO) ₂ O, 130°, 3 hr.	85 (0)

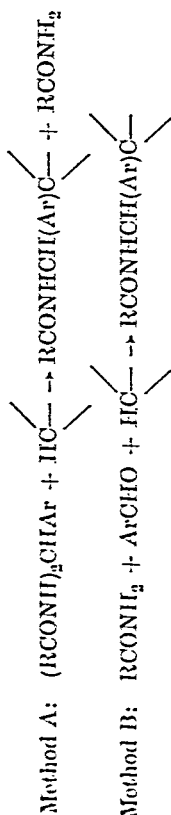
Note: References 382 to 537 are on pp. 268-269.

† The product was



† This yield is based on the combined weight of the stereoisomeric products CH₃CONHCH(Ar)CH(CO₂H)NHCOCH₃, (73).

TABLE XIV—Continued
 α -AMIDALKYLATION OF ALIPHATIC CARBON ATOMS WITH
 N,N' -ARYLDIENEISAMIDES OR THEIR PRECURSORS




Product Derived from	Method	References (Yield, %)
Ethyl carbamate, acetaldehyde, and Pentano-2,4-dione	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	108
Ethyl carbamate, cinnamaldehyde, and Pentano-2,4-dione	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	111
Ethyl acetacetate	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	111
Ethyl carbamate, benzaldehyde, and Pentano-2,4-dione	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	111
Ethyl acetacetate	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	111
Ethyl benzoylacetate	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	111
Ethyl carbamate, salicylaldehyde, and Pentano-2,4-dione	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	111
Ethyl carbamate, <i>p</i> -methoxybenzaldehyde, and Pentano-2,4-dione	B; HCl, $\text{C}_2\text{H}_5\text{OH}$	111

Note: References 382 to 537 are on pp. 266-269.

TABLE XV

AMIDOMETHYLATION OF ALIPHATIC CARBON ATOMS WITH
N-AMINOMETHYLAMIDES AND THEIR QUATERNARY SALTS

Product Derived from	Method	References (Yield, %)
$C_6H_5CONHCH_2N(CH_3)_2$ and Nitrocyclohexane	Toluene, NaOH, reflux, 50 hr.	118 (38)
Dimethyl acetamidomalonate	Toluene, NaOH, reflux, 2.5 hr.	118 (87)
Diethyl methylmalonate	Toluene, NaOH, reflux, 5.5 hr.	118 (48)
Diethyl benzylmalonate	Toluene, NaOH, reflux, 11.5 hr.	118 (68)
Diethyl phenylmalonate	Toluene, NaOH, reflux, 1 hr.	118 (100)
$C_6H_5CONHCH_2N(C_2H_5)_2$ and 1,3-Diphenylpropane-1,3-dione	Toluene, $N(C_2H_5)_3$, reflux, 30 hr.	118 (3)
Ethyl α -ethylacetoacetate	Toluene, NaOH, reflux, 30 hr.	118 (38)
Dimethyl malonate	Toluene, NaOH, reflux, 3 hr.	118 (68)
Diethyl ethylmalonate	Toluene, NaOH, reflux, 7 hr.	118 (44)
$C_6H_5O_2C(CH_3)_2CH(CN)CO_2C_2H_5$	Toluene, NaOH, reflux, 5 hr.	118 (85)
Ethyl α -phenylcyanoacetate	Toluene, NaOH, reflux, 8 hr.	118 (74)
$o-C_6H_4(CO)_2NCH_2N(CH_3)_2$ and Diethyl malonate	No solvent, NaOH, 100°, 5–15 hr.	81 (0)
Diethyl acetamidomalonate	Nylene, reflux	1*
$o-C_6H_4(CO)_2NCH_2N$  and Diethyl formamidomalonate	Nylene, 150°, 4 hr.	81 (0)
$o-C_6H_4(CO)_2NCH_2N^+(CH_3)_3 I^-$ and Cyclohexane-1,3-dione	CH_3OH , Na, reflux, 6 hr.	85 (0)
Diethyl malonate	C_2H_5OH , $NaOC_2H_5$, reflux, 7 hr.	81†
Diethyl formamidomalonate	C_2H_5OH , $NaOC_2H_5$, reflux, 5 hr.	81 (88)
Sodium cyanide	$HCON(CH_3)_2$, NaOH, reflux, 3–4 hr.	81 (76)
	$HCON(CH_3)_2$, reflux, 1 hr.	412 (81)

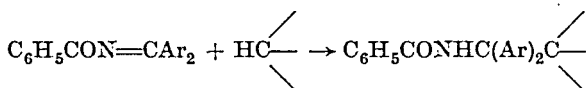
Note: References 382 to 537 are on pp. 266–269.

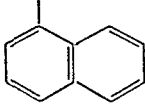
* Monodecarboxylation occurred during amidomethylation. The product isolated was $o-C_6H_4(CO)_2NCH_2CH(NHCOCH_3)CO_2C_2H_5$.

† The bisamidomethylated derivative was obtained in low yield as the sole product.

TABLE XVI

α -AMIDOALKYLATION OF ALIPHATIC CARBON ATOMS WITH
ACYLIMINES



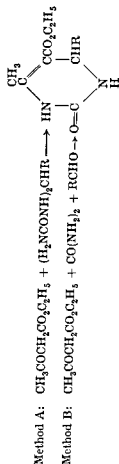
Product Derived from	Method	References (Yield, %)
$\text{C}_6\text{H}_5\text{CON}=\text{C}(\text{C}_6\text{H}_5)_2$ and Acetonitrile	LiNH_2 , liq. NH_3	120 (85)
Propionitrile	LiNH_2 , liq. NH_3	121 (50)
Butyronitrile	LiNH_2 , liq. NH_3	121 (53)
$\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{Na}$	$i\text{-C}_3\text{H}_7\text{MgCl}$, C_6H_6 /ether, reflux	19 (49)
$\text{C}_6\text{H}_5\text{CON}=\text{C}(\text{C}_6\text{H}_5)\text{C}_6\text{H}_4\text{OCH}_3$ - <i>p</i> and $\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{Na}$	$i\text{-C}_3\text{H}_7\text{MgCl}$, C_6H_6 /ether, reflux	19 (53)
$\text{C}_6\text{H}_5\text{CON}=\text{C}(\text{C}_6\text{H}_5)$ and 		
Acetonitrile	LiNH_2 , liq. NH_3	120 (59)
Propionitrile	LiNH_2 , liq. NH_3	121 (36)
Butyronitrile	LiNH_2 , liq. NH_3	121 (40)*

Note: References 382 to 537 are on pp. 266-269.

* Two diastereoisomers were isolated; one in a 37% and the other in a 3% yield.

TABLE XVII

α-AMIDOALKYLATION OF ETHYL ACETOACETATE WITH N,N'-ALKYLIDENE- AND N,N'-ARYLIDENE-BISUREAS OR THEIR PRECURSORS. THE BIGINELLI PYRIMIDINE SYNTHESIS

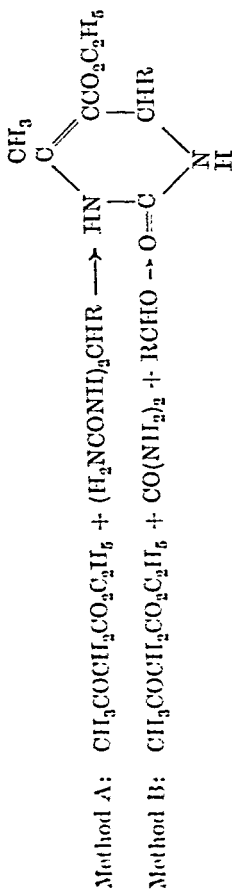


Product Derived from Urea and	Method	References (Yield, %)
Formaldehyde	A; HCl, CH ₃ CO ₂ H, 120° A; 120°, 5-8 hr.	126 (18) 124
Acetaldehyde	B; HCl, C ₂ H ₅ OH, 80°, 3 hr. B; HCl, dioxane, 100°, 2 hr. B; 100°, 2-3 hr.	126 (26) 126 (47) 124
Heptanal	B; HCl, C ₂ H ₅ OH, 80°, 5.5 hr.	126 (7)
β-Phenylpropionaldehyde	B; CH ₃ CO ₂ H, 25°, 450 hr.	126 (13)
Cinnamaldehyde	A; C ₂ H ₅ OH, 80° B; C ₂ H ₅ OH, 80°, 2 hr. B; CH ₃ CO ₂ H, 25°	123 122 126 (71)

Note. References 382 to 537 are on pp. 266-269.

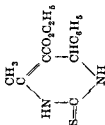
TABLE XVII—Continued
 α -AMIDOMETHYLATION OF ETHYL ACETOACETATE WITH N,N' -ALKYLIDENE- AND N,N' -ARYLIDENE-
 BISUREAS OR THEIR PRECURSORS. THE BIGINELLI PYRIMIDINE SYNTHESIS

Product Derived from Urea and	Method	References (Yield, %)
Benzaldehyde	A: C_2H_5OH , 80° , 5–6 hr. B: C_2H_5OH , 80° , 2 hr. B: HCl , C_2H_5OH , 80° , 3 hr. B: 120° , 6 hr. B: $CS(NH_2)_2$, C_2H_5OH , reflux B: HCl , C_2H_5OH , 80° , 6 hr. B: HCl , C_2H_5OH , 80° , 3 hr. B: HCl , CH_3CO_2H , 120° , 3 hr. A, B: C_2H_5OH , 80° , 2 hr. B: HCl , C_2H_5OH , 80° , 3 hr.	122, 125 122, 125 (56) 126 (78) 125 (60) 125* 124, 126 (56) 126 (31) 126 (58) 122, 123 126 (19)
<i>m</i> -Nitrobenzaldehyde		
<i>p</i> -Nitrobenzaldehyde		
Salicylaldehyde		



<i>p</i> -Hydroxybenzaldehyde	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (66)
3,5-Diortho-4-hydroxybenzaldehyde	B; HCl, CH ₃ CO ₂ H, 120°, 2.25 hr.	126 (11)
<i>p</i> -Anisaldehyde	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (61)
2,4-Dihydroxybenzaldehyde	B; CH ₃ CO ₂ H, 25°, 120 hr.	126 (34)
Vanillin	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (42)
Veratraldehyde	B; HCl, C ₂ H ₅ OH, 80°, 2 hr.	126 (47)
Piperonal	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (49)
2,4,6-Trimethoxybenzaldehyde	B; HCl, C ₂ H ₅ OH, 80°, 2 hr.	126 (38)
<i>p</i> -Isopropylbenzaldehyde	A, B; C ₂ H ₅ OH, 80°	123
2-Furaldehyde	A; HCl, C ₂ H ₅ OH, 80°	124
	B; C ₂ H ₅ OH, 80°, 2 hr.	122, 123, 126 (36)

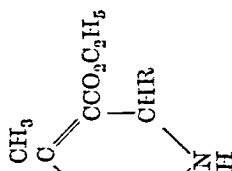
Note: References 382 to 537 are on pp. 266-269.



• Thionurea replaced urea to give the corresponding product

TABLE XVII—Continued
 α -AMINOALKYLATION OF ETHYL ACETOACETATE WITH N,N'-ALKYLIDENE- AND N,N'-ARYLIDENE-
 HISTIDINES OR THEIR PRECURSORS. THE BIGNELLI PYRIMIDINE SYNTHESIS

Product	Derived from Urea and	Method	References (Yield, %)
Benzaldehyde		A; C_2H_5OH , 80° , 5–6 hr. B; C_2H_5OH , 80° , 2 hr. B; HCl , C_2H_5OH , 80° , 3 hr. B; 120° , 6 hr. B; $CS(NH_2)_2$, C_2H_5OH , reflux B; HCl , C_2H_5OH , 80° , 6 hr. B; HCl , C_2H_5OH , 80° , 3 hr. B; HCl , CH_3CO_2H , 120° , 3 hr. A, B; C_2H_5OH , 80° , 2 hr. B; HCl , C_2H_5OH , 80° , 3 hr.	122, 125 122, 125 (56) 126 (78) 125 (60) 125* 124, 126 (56) 126 (31) 126 (58) 122, 123 126 (19)
m-Nitrobenzaldehyde			
p-Nitrobenzaldehyde			
Salicylaldehyde			

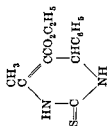


Method A: $CH_3COCH_2CO_2C_2H_5 + (H_2NCONH)_2CHR \longrightarrow$

Method B: $CH_3COCH_2CO_2C_2H_5 + CO(NH_2)_2 + RCHO \rightarrow O=C$

<i>p</i> -Hydroxybenzaldehyde	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (66)
3,5-Diiodo-4-hydroxybenzaldehyde	B; HCl, CH ₃ CO ₂ H, 120°, 2.25 hr.	126 (11)
<i>p</i> -Anisaldehyde	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (61)
2,4-Dihydroxybenzaldehyde	B; CH ₃ CO ₂ H, 25°, 120 hr.	126 (34)
Vanillin	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (42)
Veratraldehyde	B; HCl, C ₂ H ₅ OH, 80°, 2 hr.	126 (47)
Piperonal	B; HCl, C ₂ H ₅ OH, 80°, 3 hr.	126 (49)
2,4,6-Trimethoxybenzaldehyde	B; HCl, C ₂ H ₅ OH, 80°, 2 hr.	126 (38)
<i>p</i> -Isopropylbenzaldehyde	A, B; C ₂ H ₅ OH, 80°	123
2-Furaldehyde	A; HCl, C ₂ H ₅ OH, 80°	124
	B; C ₂ H ₅ OH, 80°, 2 hr.	122, 123, 126 (36)

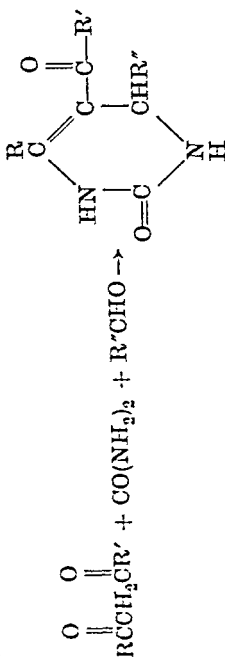
Note: References 382 to 537 are on pp. 266-269.



* Thiourea replaced urea to give the corresponding product

TABLE XVIII

α -AMIDOALKYLATION OF ACTIVE METHYLENE COMPOUNDS OTHER THAN ETHYL ACETOACETATE WITH UREA AND ALDEHYDES. THE BIGINELLI PYRIMIDINE SYNTHESIS

References
(Yield, %)

Method

Product Derived from Urea

Pentane-2,4-dione and	HCl, C ₂ H ₅ OH, reflux, 5 hr.	128 (32)
Propionaldehyde	HCl, C ₂ H ₅ OH, reflux, 4 hr.	128 (0)
Isovaleraldehyde	HCl, C ₂ H ₅ OH, reflux, 4 hr.	128 (0)
Heptanal	CH ₃ CO ₂ H, 100°, 3 hr.	128 (92)
Cinnamaldehyde	HCl, C ₂ H ₅ OH, reflux, 3.5 hr.	128 (55)
Benzaldehyde	HCl, C ₂ H ₅ OH, reflux, 3 hr.	128 (70)
<i>m</i> -Nitrobenzaldehyde	HCl, C ₂ H ₅ OH, reflux, 2 hr.	128 (49)
Salicylaldehyde	HCl, C ₂ H ₅ OH, reflux, 3.5 hr.	128 (40)
<i>o</i> -Methoxybenzaldehyde	HCl, C ₂ H ₅ OH, reflux, 1 hr.	128 (44)
3,4-Dimethoxybenzaldehyde	HCl, C ₂ H ₅ OH, reflux, 3 hr.	128 (40)
<i>p</i> -(CH ₃) ₂ NC ₆ H ₄ CHO	HCl, C ₂ H ₅ OH, reflux, 3.5 hr.	128 (65)
4-Hydroxy-3-methylbenzaldehyde	CH ₃ CO ₂ H, 100°, 2 hr.	128 (89)
2-Furaldehyde		

Cyclohexane-1,3-dione and
n-Butyraldehyde
o-Chlorobenzaldehyde
p-Methoxybenzaldehyde
p-(CH₃)₂NC₆H₄CHO
 1-Phenylbutane-1,3-dione and
 Benzaldehyde
o-Chlorobenzaldehyde
m-Nitrobenzaldehyde
p-Hydroxybenzaldehyde
p-Methoxybenzaldehyde
 Ethyl benzoylacetate and
 Acetaldehyde

HCl, C₂H₅OH, reflux, 2.5 hr. 130 (0)
 HCl, C₂H₅OH, reflux, 3.5 hr. 130 (80)
 HCl, C₂H₅OH, reflux, 3 hr. 130 (0)
 HCl, C₂H₅OH, reflux, 3 hr. 130 (0)

 HCl, C₂H₅OH, reflux, 3 hr. 129 (51)*
 HCl, C₂H₅OH, reflux, 2 hr. 129 (38)*
 HCl, C₂H₅OH, reflux, 2 hr. 129 (42)*
 HCl, C₂H₅OH, reflux, 2 hr. 129 (53)*
 HCl, C₂H₅OH, reflux, 2 hr. 129 (50)*

 HCl, CH₃CO₂H, 100°, 24 hr. 413

Note: References 382 to 537 are on pp. 266-269.

* The relative positions of R and R' in the product were not established.

TABLE XIX

AMIDOMETHYLATION OF POTASSIUM CYANIDE WITH
 ARENESULFONAMIDOMETHANESULFONATES
 $\text{ArSO}_2\text{NHCH}_2\text{SO}_3\text{Na} + \text{KCN} \rightarrow \text{ArSO}_2\text{NHCH}_2\text{CN} + \text{NaKSO}_3$

Product Derived from	Method	References (Yield, %)
C ₆ H ₅ SO ₂ NHCH ₂ SO ₃ Na	H ₂ O	132
<i>m</i> -C ₆ H ₄ (SO ₂ NHCH ₂ SO ₃ Na) ₂	H ₂ O	132 (75)

Note: References 382 to 537 are on pp. 266-269.

TABLE XX

N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES, IMIDES, AND SULFONAMIDES

References
(Yield, %)

N-Methylol Derivative

Method*

Of Aliphatic Amides $\text{HCONHCH}_2\text{OH}$ $\text{HCON}(\text{CH}_3)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CONHCH}_2\text{OH}$ $\text{CH}_3\text{CON}(\text{CH}_3)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CON}(\text{C}_3\text{H}_7-n)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CON}(\text{C}_3\text{H}_7-i)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CON}(\text{CH}_2\text{C}_6\text{H}_5)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CON}(\text{CH}_2\text{NHCOCH}_3)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CON}(\text{CH}_2\text{CH}_2\text{NHCOCH}_3)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CON}(\text{CH}_2\text{CH}_2\text{NHCOCH}_3)\text{CH}_2\text{OH}$ $\text{CH}_3\text{CONHCH}_2\text{OH}$ $\text{CCl}_3\text{CONHCH}_2\text{OH}$ $\text{CH}_2\text{BrCONHCH}_2\text{OH}$ $\text{CH}_2\text{ICONHCH}_2\text{OH}$ $o\text{-CH}_3\text{OC}_6\text{H}_4\text{OCH}_2\text{CONHCH}_2\text{OH}$  $\text{CH}_3\text{CH}(\text{CH}_2\text{CONHCH}_2\text{OH})_2$

Formalin, baso

20% aq. CH_2O , 60° $(\text{CH}_2\text{O})_x$, heat20% aq. CH_2O , 60°

Formalin, baso

20% aq. CH_2O , 60° $(\text{CH}_2\text{O})_x$, heat $(\text{CH}_2\text{O})_x$, baso20% aq. CH_2O , 60° $(\text{CH}_2\text{O})_x$, 120-145° $(\text{CH}_2\text{O})_x$, baso, 110° $(\text{CH}_2\text{O})_x$, baso, 110° $(\text{CH}_2\text{O})_x$, baso, 110° 20% aq. CH_2O , 60° 20% aq. CH_2O , 60° 20% aq. CH_2O , 60°

Formalin, baso

Formalin, acid

Formalin, baso

Formalin, acid

Formalin, acid

Formalin, acid

Formalin, baso

 $\text{RCON}(\text{CH}_2\text{OH})_2, \text{H}_2\text{O}$

22

154

414

154

23

154

96, 414

217, 415

154

32 (good), 244

32

32

32

154

154

154

11 (100), 52

416

264 (100)

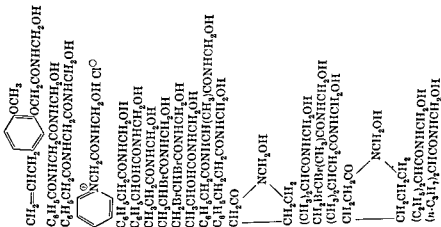
416

416, 417

416, 417

418

42



$\text{RCON}(\text{CH}_2\text{OH})_2, \text{H}_2\text{O}$

Formalin, base

Formalin, base

$\text{CH}_2\text{ClCONHCH}_2\text{OH}$, pyridine

Formalin, base

Formalin, base

Formalin, base

Formalin, acid

$\text{CH}_2=\text{CHCONHCH}_2\text{OH}$, Br_2

Formalin, base

Formalin, base

Formalin, base

Formalin, base, 85°

$(\text{CH}_2\text{O})_2$, 120°

Formalin, base

Formalin, base

Formalin, base

Formalin, base, 85°

$(\text{CH}_2\text{O})_2$, base, 140°

$(\text{CH}_2\text{O})_2$, 110°

Formaldehyde

Formalin, base

Formalin, base

42

79

79 (86)

312 (30)

388 (83)

43

153 (90)

416, 417

253

43

79 (87)

79

177, 184 (85)

33 (80)

153

253 (51)

54, 418, 419 (65)

184 (70)

310 (67)

33

420


419 (80)








153 (82)

Note: References 382 to 537 are on pp. 206-269.

* Unless otherwise indicated, the amide or imide is an unnamed reactant.

TABLE XX—Continued
N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES, IMIDES, AND SULFONAMIDES

N-Methylol Derivative	Method*	References (Yield, %)
<i>Of Aliphatic Amides (contd.)</i>		
$n\text{-C}_{11}\text{H}_{23}\text{CONHCH}_2\text{OH}$	Formalin, base, heat	222 (88)
$\text{C}_7\text{H}_{13}(\text{CH}_2)_4\text{CONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, base, C_6H_6 , 50°	217 (100)
$n\text{-C}_{17}\text{H}_{35}\text{CONHCH}_2\text{OH}$	Formalin, base, 70°	138 (83), 139, 140, 312
	$(\text{CH}_2\text{O})_x$, 00°	217 (85)
$n\text{-C}_{17}\text{H}_{35}\text{CON}(\text{CH}_3)\text{CH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, heat	139
$n\text{-C}_{21}\text{H}_{43}\text{CONHCH}_2\text{OH}$	Formalin, base	235
$\text{CH}_3\text{CHCONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, base	254 (70), 421 (87), 422, 423
$\alpha\text{-ClC}_6\text{H}_4\text{CH}_2\text{CHCONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, base	312 (91)
 $\text{CH}_2\text{CHCONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, NaOC_2H_5 , CCl_4	35 (82)
$\text{CH}_3\text{CH}(\text{CH}_3)\text{CONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, base	254 (70), 421 (83), 424 (64)
$(\text{CH}_3)_2\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, NaOC_2H_5 , CCl_4	422 (77)
$\text{CH}_2=\text{CH}(\text{CH}_2)_6\text{CONHCH}_2\text{OH}$	Formalin, base	382 (96)
$\text{CH}_3(\text{CH}_2)_7\text{CH}(\text{CH}_3)_2\text{CONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, heat	139
$\text{CH}_3(\text{CH}(\text{CH}_3)\text{CONHCH}_2\text{OH})_2$	Formalin, base	389 (78), 423
<i>Of Aromatic Amides</i>		
$\text{C}_6\text{H}_5\text{CONHCH}_2\text{OH}$	Formalin, base	1, 10 (100), 52, 79, 88
	Formalin, acid	263, 425 (64)
$\text{C}_6\text{H}_5\text{CON}(\text{CH}_3)\text{CH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, base, 110°	32
$2,4\text{-Cl}_2\text{C}_6\text{H}_3\text{CONHCH}_2\text{OH}$	Formalin, base	96 (75)
$\alpha\text{-O}_2\text{NC}_6\text{H}_4\text{CONHCH}_2\text{OH}$	Formalin, base	221
$m\text{-O}_2\text{NC}_6\text{H}_4\text{CONHCH}_2\text{OH}$	Formalin, base	221

$p\text{-O}_2\text{NC}_6\text{H}_4\text{CONHCH}_2\text{OH}$	Formalin, base (CH_2O) _x , heat	221 (56) 139
$o\text{-HOC}_6\text{H}_4\text{CONHCH}_2\text{OH}$	Formalin, base	25 (93), 418
$p\text{-HOC}_6\text{H}_4\text{CONHCH}_2\text{OH}$	Formalin, acid	25 (62), 425
$p\text{-CH}_3\text{C}_6\text{H}_4\text{CONHCH}_2\text{OH}$	Formalin, base	418
<i>Of Heteroaromatic Amides</i>	Formalin, base	418
	(CH_2O) _x , base	35
	Formalin, base, heat	426
	Formalin, base	426
	Formalin, base	426
	Formalin, heat	427 (69)
	RCONHCH ₂ OH, CH ₃ Cl	427 (78)
	Formalin, 60°	427 (59)
	RCONHCH ₂ OH, C ₈ H ₁₇ OSO ₂ CH ₃	427 (61)

Note. References 382 to 537 are on pp. 266-269.

• Unless otherwise indicated, the amide or imide is an unnamed reactant.

TABLE XX—Continued
N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES, IMIDES, AND SULFONAMIDES

N-Methylol Derivative	Method*	References (Yield, %)
<i>of Heteroaromatic Amides (contd.)</i>		
	RCONHCH ₂ OH, <i>n</i> -C ₁₂ H ₂₅ Br	427 (68)
	Formalin, 30° RCONHCH ₂ OH, <i>n</i> -C ₁₆ H ₃₃ Br	427 (66) 427 (79)
	Formalin, 50° RCONHCH ₂ OH, CH ₃ ClCO ₂ H	427 (73) 427
	Formalin, 40° RCONHCH ₂ OH, CH ₃ ClCONH ₂	427 (80) 427 (84)
	Formalin, base, 80°	428
	Formalin, base, 80°	428 (97)

	428 (95)
	428 (95)
	429 (80) 430 (66)
	426
	426
	242
	66 (100)
	8

Formalin, base, 100°

Formalin, NaHCO₃, 50°
Formalin, 100°

Formalin, base, heat

Formalin, base, heat

Formalin, base

Formalin, base

N-Methylolmaleimide, HCl

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the amide or imido is an unnamed reactant.

TABLE XX—Continued
N-MONOMETHYLOL DERIVATIVES OF CARBOXYAMIDES, IMIDES, AND SULFONAMIDES

N-Methylol Derivative	Method*	References (Yield, %)
<i>Of Imides (contd.)</i> $\begin{array}{c} \text{C}_6\text{H}_5\text{CONHCHCO} \\ \qquad \qquad \\ \text{NCH}_2\text{OH} \\ \\ \text{CH}_2\text{CO} \end{array}$	Formalin	431 (92)
$\begin{array}{c} \text{CHCO} \\ \diagup \quad \diagdown \\ \text{NCH}_2\text{OH} \\ \diagdown \quad \diagup \\ \text{CHCO} \end{array}$	Formalin, base, 35°	8 (75), 432
$\begin{array}{c} \text{CO} \qquad \text{CO} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{CH}_2 \qquad \text{NCH}_2\text{OH} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{CO} \qquad \text{CO} \end{array}$		433
<i>o</i> -C ₆ H ₄ (CO) ₂ NCH ₂ OH	Formalin, heat	1, 84 (96), 434, 435 (90)
	10–15% aq. CH ₂ O, heat	104 (excellent)
$\begin{array}{c} \text{NO}_2 \\ \\ \text{CO} \qquad \text{CO} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{C}_6\text{H}_2 \qquad \text{NCH}_2\text{OH} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{CO} \qquad \text{CO} \end{array}$	Formalin, 100°	436
$\begin{array}{c} \text{O}_2\text{N} \qquad \text{CO} \\ \qquad \diagup \quad \diagdown \\ \text{C}_6\text{H}_3 \qquad \text{NCH}_2\text{OH} \\ \diagdown \quad \diagup \\ \text{CO} \end{array}$	Formalin, 100°	436
$\begin{array}{c} \text{SO}_2 \\ \\ \text{CO} \qquad \text{CO} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{C}_6\text{H}_2 \qquad \text{NCH}_2\text{OH} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{CO} \qquad \text{CO} \end{array}$	Formalin, 100° Formalin, heat	99 (69) 182 (81), 437

$o\text{-C}_6\text{H}_4(\text{CO})_2\text{N} \begin{array}{c} \text{SO}_2\text{NCH}_2\text{OH} \\ \\ \text{CH}_3\text{CO} \end{array}$	Formalin, base	157
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{N} \begin{array}{c} \text{SO}_2\text{NCH}_2\text{OH} \\ \\ (\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CO} \end{array}$ <p><i>Of Sulfonamides</i></p> $\text{C}_6\text{H}_5\text{SO}_2\text{NHCH}_2\text{OH}$ $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCH}_2\text{OH}$	Formalin, base	157
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{N} \begin{array}{c} \text{SO}_2\text{N} \begin{array}{c} \text{CH}_2\text{OH} \\ \\ \text{CH}_2\text{OH} \end{array} \end{array}$	Formalin, base Formalin, base	155 (60), 156 155 (93), 156 (60), 438
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{N} \begin{array}{c} \text{SO}_2\text{N} \begin{array}{c} \text{CH}_2\text{OH} \\ \\ \text{CH}_2\text{OH} \end{array} \end{array}$	Formalin, base	157
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{N} \begin{array}{c} \text{SO}_2\text{N} \begin{array}{c} \text{CH}_2\text{OH} \\ \\ \text{CH}_2\text{OH} \end{array} \end{array}$	Formalin, base	157

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the amide or imide is an unnamed reactant.

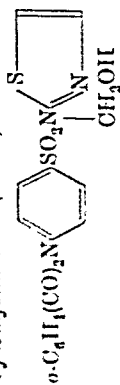
TABLE XX—Continued
N-MONOMETHYLOL DERIVATIVES OF CARBOXAMIDES, IMIDES, AND SULFONAMIDES

References
(Yield, %)

N-Methylol Derivatives

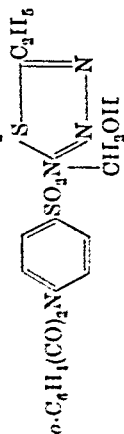
Method*

Of Sulfonamides (contd.)



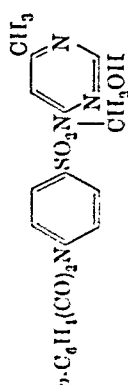
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Formalin, base



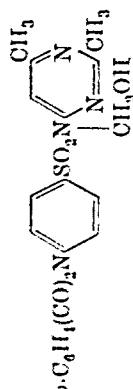
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Formalin, base



157

Formalin, base




157

Formalin, base

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the amide or imide is an unnamed reactant.

TABLE XXI
POLY-N-METHYLOL DERIVATIVES OF MONO- AND POLY-CARBOXAMIDES

N-Methylol Derivatives	Method*	References (Yield, %)
<i>Of Monocarboxamides</i>		
	Formalin, base	41 (100)
$\text{CH}_2=\text{CH}-\text{C}_6\text{H}_4-\text{OCH}_3$ $\text{OCH}_2\text{CON}(\text{CH}_2\text{OH})_2$	Formalin, base	42
$\text{CH}_2=\text{CH}-\text{C}_6\text{H}_4-\text{OCH}_3$ $\text{OCH}_2\text{CON}(\text{CH}_2\text{OH})_2$	Formalin, base	42
<i>Of Polycarboxamides</i>		
$(\text{CONHCH}_2\text{OH})_2$	Formalin, base	35 (47)
$(\text{C}_2\text{H}_5)_2\text{C}(\text{CONHCH}_2\text{OH})_2$	Formalin, base	263 (100)
$(\text{CH}_2)_2(\text{CONHCH}_2\text{OH})_2$	Formalin, base	24 (80)
$\text{CHOHCONHCH}_2\text{OH}$	Formalin, base	43 (70)
$\text{CHOHCONHCH}_2\text{OH}$ $(\text{CH}_3)_4\text{C}(\text{CONHCH}_2\text{OH})_2$	Formalin, base	406 (71)
$(\text{CH}_2)_4(\text{CONHCH}_2\text{OH})_2$	Formalin, base	406 (50)
$(\text{CH}_2)_7(\text{CONHCH}_2\text{OH})_2$	Formalin, base	406 (60)

Note: References 382 to 537 are on pp. 266-269.

* The amido is an unnamed reactant.

TABLE XXI—Continued
POLY-N-METHYLOL DERIVATIVES OF MONO- AND POLY-CARBOXAMIDES

N-Methylol Derivatives	Method*	References (Yield, %)
<i>Of Polycarboxamides (contd.)</i>		
$(\text{CH}_2)_4(\text{CONHCH}_2\text{OH})_2$ $\text{CH}_2\text{CONHCH}_2\text{OH}$	Formalin, base	406 (81)
$\text{HOOCNHCH}_2\text{OH}$ $\text{CH}_2\text{CONHCH}_2\text{OH}$	Formalin, base	43 (20)
$\text{HOCH}_2\text{N}(\text{CH}_2\text{OH})\text{C}(=\text{O})\text{CH}_2\text{N}(\text{CH}_2\text{OH})\text{C}(=\text{O})\text{CH}_2\text{OH}$	Formalin Formalin, base Formalin, acid	1, 65 (90) 79 79 (0)
$\text{CH}_2\text{N}(\text{CHO})\text{CH}_2\text{OH}$ $[\text{CH}_2\text{N}(\text{CHO})\text{CH}_2\text{OH}]_2$ $\text{CH}_2\text{CHN}(\text{CHO})\text{CH}_2\text{OH}$	20% aq. CH_3O , 60° 20% aq. CH_3O , 60°	154 154
$\text{CH}_2\text{N}(\text{CHO})\text{CH}_2\text{OH}$ $\text{CH}_2\text{CH}_2\text{N}(\text{CHO})\text{CH}_2\text{OH}$ $\text{HOCH}_2\text{CH}_2\text{N}(\text{CHO})\text{CH}_2\text{OH}$	20% aq. CH_3O , 60° 20% aq. CH_3O , 60° 20% aq. CH_3O , 60°	154 154 154



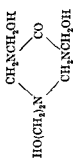
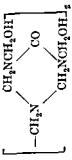

$\text{HCON}[\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CHO})\text{CH}_2\text{OH}]_2$ $\text{HCCONHCH}_2\text{OH}$	20% aq. CH_2O , 60°	154
$\text{HCCONHCH}_2\text{OH}$ $\text{HOCH}_2\text{NHCOCH}$		423
$\text{HCCONHCH}_2\text{OH}$ $\text{OCH}_2\text{CONHCH}_2\text{OH}$ $\text{OCH}_2\text{CONHCH}_2\text{OH}$	Formalin, acid	254 (53)
$\text{OCH}_2\text{CONHCH}_2\text{OH}$	Formalin, base	254 (49)
$\text{OCH}_2\text{CONHCH}_2\text{OH}$	Formalin, base	439
$\text{OCH}_2\text{CONHCH}_2\text{OH}$ $\text{OCH}_2\text{CONHCH}_2\text{OH}$	Formalin, base	439
HOCH_2NHCO CONHCH_2OH	Formalin, base 100°	428 (50)
HOCH_2NHCO CONHCH_2OH CH_3NCH_3	Formalin, NaHCO_3 , 100°	428

Note. References 382 to 537 are on pp. 268-269.

* The amide is an unnamed reactant.

TABLE XXII
N-MONO- AND N,N'-DI-METHYLOL DERIVATIVES OF CARBAMYL COMPOUNDS

N-Methylol Derivatives	Method *	References (Yield, %)
$\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}_2\text{OH}$	Formalin, acid	153 (60)
$n\text{-C}_{12}\text{H}_{25}\text{O}_2\text{CNHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, pyridine, 90°	235
$\text{C}_6\text{H}_5\text{CH}_2\text{NHCOCH}_2\text{NCH}_2\text{OH}$ $\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$	CH_3CO $\text{C}_6\text{H}_5\text{CH}_2\text{O}_2\text{CN}$ O, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$ CH_2	344 (91)
$\text{H}_2\text{NCONHCH}_2\text{OH}$	Formalin, base	153, 440-443
	Formalin, pH 8.5	144 (20)
	$(\text{CH}_2\text{O})_x$, base	444
	Formalin, base	153, 442, 445 (90)
	$(\text{CH}_2\text{O})_x$, base, 15°	444 (100), 446
$\text{CO}(\text{NHCH}_2\text{OH})_2$	Formalin	440, 443
	$\text{CO}(\text{NHCH}_2\text{OH})_2$, base	62
$\text{O}(\text{CH}_2\text{NHCONHCH}_2\text{OH})_2$	Formalin, base	153 (71)
$\text{CH}_3\text{NHCON}(\text{CH}_3)\text{CH}_2\text{OH}$	Formalin, base	153 (75)
$(\text{CH}_3)_2\text{NCONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, base	54, 55, 62
$\text{C}_6\text{H}_5\text{NHCONHCH}_2\text{OH}$	$(\text{CH}_2\text{O})_x$, base	55
$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCONHCH}_2\text{OH}$	Formalin, base	219 (10)
$\text{H}_2\text{NCONHCH}_2\text{NHCONHCH}_2\text{OH}$	Formalin, base	219 (20)
$\text{CH}_3(\text{NHCONHCH}_2\text{OH})_2$	Formalin, base	265 (96)
$\text{H}_2\text{N}(\text{SNHCH}_2\text{OH})_2$	Formalin, base	265 (100)
$\text{CS}(\text{NHCH}_2\text{OH})_2$	Formalin, base	

	Formalin, base	447 (60), 448, 449, 450 (66)
	Formalin, base, 70° Formalin	451 (97) 452a
	Formalin	452a
	Formalin	452a
	Formalin, heat	185 (76)

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the carbamyl compound is an unnamed reactant.

TABLE XXII—Continued
N-Mono- and N,N'-Di-methylol Derivatives of Carbamyl Compounds

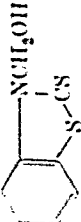
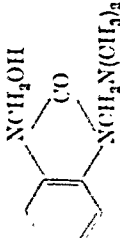
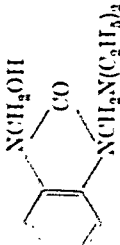
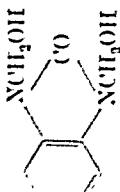
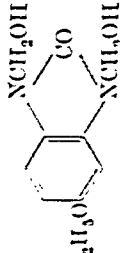
N-Methylol Derivatives	Method*	References (Yield, %)
$\begin{array}{c} \text{CONCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ (\text{CH}_3)_2\text{CNH} \end{array}$	Formalin, heat	453 (99)
$\begin{array}{c} \text{CONCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5\text{CHNH} \end{array}$	Formalin, heat	187 (62)
$\begin{array}{c} \text{OC—NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5\text{C}(\text{CH}_3)\text{NH} \end{array}$	Formalin, heat	187 (66)
$\begin{array}{c} \text{OC—NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5\text{C}(\text{C}_2\text{H}_5)\text{NH} \end{array}$	Formalin, heat	187 (67)
$\begin{array}{c} \text{CONCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5\text{C}(\text{C}_2\text{H}_5)\text{NH} \end{array}$	Formalin, heat	187 (67)
$\begin{array}{c} \text{C—NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{CH}_2\text{NCH}_3 \end{array}$	Formalin, creatine Formalin, creatinine	454 (90) 454 (80)

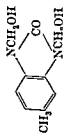
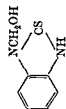
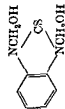
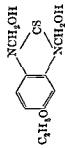
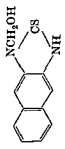
$\begin{array}{c} \text{CHNCH}_2\text{OH} \\ \diagdown \quad \diagup \\ \text{CS} \\ \diagup \quad \diagdown \\ \text{CHNCH}_2\text{OH} \end{array}$	Formalin, base	455 (72)
$\begin{array}{c} \text{CHCO} \\ \diagdown \quad \diagup \\ \text{CH}_2\text{C} \\ \diagup \quad \diagdown \\ \text{NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{NHCS} \end{array}$	Formalin, heat	239
$\begin{array}{c} \text{CHCO} \\ \diagdown \quad \diagup \\ \text{n-C}_3\text{H}_7\text{C} \\ \diagup \quad \diagdown \\ \text{NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{NHCS} \end{array}$	Formalin, heat	239
$\begin{array}{c} \text{NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{O} \\ \diagdown \quad \diagup \\ \text{CO} \end{array}$	Formalin, 100°	194 (82)
$\begin{array}{c} \text{NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{O} \\ \diagdown \quad \diagup \\ \text{CS} \end{array}$	Formalin, heat	181 (75)
$\begin{array}{c} \text{NCH}_2\text{OH} \\ \diagup \quad \diagdown \\ \text{O} \\ \diagdown \quad \diagup \\ \text{CS} \end{array}$ <p>(DL-trans)</p>	Formalin, 100°	178 (70)

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the carbamyl compound is an unnamed reactant.

TABLE XXII—Continued
N-MONO- AND N,N'-DI-METHYLOL DERIVATIVES OF CARBAMYL COMPOUNDS

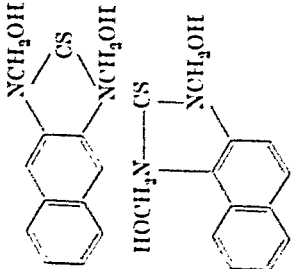
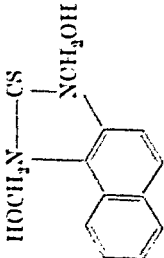
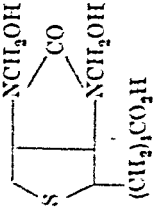
N-Methylol Derivatives	Method*	References (Yield, %)
	Formalin, heat	183 (96), 189 (84)
	Formalin, (CH ₃) ₂ NH	180 (54)
	Formalin, (C ₂ H ₅) ₂ NH	180 (30)
	Formalin, 100°	180 (80), 238, 456
	Formalin, 100°	237

	Formalin, heat	450 (71)
	Formalin, base	457 (77)
	Formalin, 100°	179 (83), 238
	Formalin, 100°	237
		239

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the carbamyl compound is an unnamed reactant.

TABLE XXII—Continued
 N-Mono- and N,N'-Di-methylol Derivatives of Carbamyl Compounds

N-Methylol Derivatives	Method*	References (Yield, %)
	239, 457	239, 457
	Formalin, 100°	241
	(CH ₂ O) _x , base, 50°	458 (45)

Note: References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the carbamyl compound is an unreacted reagent.

TABLE XXIII

α-HYDROXYALKYL DERIVATIVES OF CARBOXYAMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $RCONH_2 + R'CHO \rightarrow RCONHCHOHR'$

(R' = haloalkyl)

α-Alkylolamide Derivative	References (Yield, %)	α-Alkylolamide Derivative	References (Yield, %)
<i>Of Aliphatic Monoamides</i>			
HCONHCHOHCH ₃	95, (100), 459	CH ₃ CO NCHOHCHCH ₃ CH ₃ CH ₃	101 (60), 467
HCONHCHOHCH ₂ Br	207	n-C ₄ H ₉ CONHCHOHCH ₃	164, 460 (78)
C ₂ H ₅ O ₂ CONHCHOHCH ₃	463	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₃	460 (89)
CH ₃ CONHCHOHCH ₂ CH ₃	160, 163, 229	i-C ₄ H ₉ CONHCHOHCH ₃	460 (41)
CH ₃ CONHCHOHCH ₂ CH ₂ Br	208	i-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ Br	207
CH ₃ CONHCHOHCH ₂ CH ₂ CH ₃	95, 158, 460 (80), 461, 462	i-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ Br	460 (14)
CH ₃ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₃	463	(CH ₃) ₂ CHCH ₂ CONHCHOHCH ₃	468
CH ₃ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460, 463 (70), 464	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₃	164, 460 (89)
CH ₃ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	465 (50), 466	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₃	207
CH ₃ CH ₂ CONHCHOHCH ₃	460 (43)	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460 (82)
C ₂ H ₅ CH ₂ CONHCHOHCH ₃	164, 466 (77)	(C ₂ H ₅) ₂ CHCONHCHOHCH ₃	460 (78)
C ₂ H ₅ CH ₂ CONHCHOHCH ₂ CH ₃	166	(C ₂ H ₅) ₂ CHCONHCHOHCH ₂ CH ₃	460 (42)
NCCH ₃ CONHCHOHCH ₃	466 (37)	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₃	164, 460 (81)
C ₂ H ₅ CONHCHOHCH ₃	163	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	207
C ₂ H ₅ CONHCHOHCH ₂ CH ₃	164, 460 (76)	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460 (72)
C ₂ H ₅ CONHCHOHCH ₂ CH ₂ CH ₃	207	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460 (100)
C ₂ H ₅ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₃	460 (65)	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	207
n-C ₄ H ₉ CONHCHOHCH ₃	460 (79)	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460 (66)
n-C ₄ H ₉ CONHCHOHCH ₂ CH ₃	166	n-C ₄ H ₉ CH(C ₂ H ₅)CONHCHOHCH ₃	460 (88)
C ₂ H ₅ CH(C ₂ H ₅)CONHCHOHCH ₃	460 (66)	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460 (76)
i-C ₄ H ₉ CONHCHOHCH ₃	466 (28)	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460 (57)
i-C ₄ H ₉ CONHCHOHCH ₂ CH ₃	164	n-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	460 (59)
i-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₃	207		207
i-C ₄ H ₉ CONHCHOHCH ₂ CH ₂ CH ₂ CH ₃	466 (76)		460 (43)

Note. References 382 to 537 are on pp 266-269

* This substance was prepared by an indirect method.

Of Heteroaromatic Amides



204 (86)



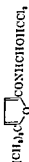
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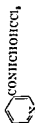
204 (84)



204 (74)



204 (91)

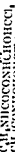


471

Of Diarbazomides



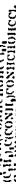
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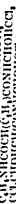
163



166



163



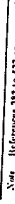
286



163



163

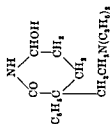


166

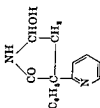
Note. References 282 to 337 are on pp. 266-289.

* This substance was prepared by an indirect method.

Of Lactams



174



174 (30)



175 (66)





175 (50)




175 (23)




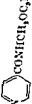
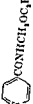
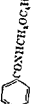
Of Carbonyl Compounds (cont'd.)

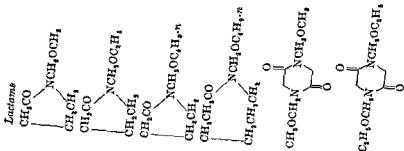
NHCONHCl	161	$\text{C}_6\text{H}_5\text{NHCONHCONHCl}$	73, 161 (83)
$\text{NHCH(OC}_2\text{H}_5\text{)CCl}$		$\text{C}_6\text{H}_5\text{NHCONHCONHCH}_2\text{Br}$	163
NHCONHCl		$\text{C}_6\text{H}_5\text{NHCONHCONH(CH}_2\text{)}_2\text{Cl}$	73
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$	161	$p\text{-ClC}_6\text{H}_4\text{NHCONHCONHCl}$	73
NHCONHCl		$m\text{-O}_2\text{NC}_6\text{H}_4\text{NHCONHCONHCl}$	227
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$p\text{-O}_2\text{NC}_6\text{H}_4\text{NHCONHCONHCl}$	227
NHCONHCl		$o\text{-CH}_3\text{C}_6\text{H}_4\text{NHCONHCONHCl}$	227
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCONHCONHCl}$	227
NHCONHCl		$(\text{C}_6\text{H}_5)_2\text{NCONHCONHCl}$	163
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$(\text{C}_6\text{H}_5)_3\text{NCONHCONHCH}_2\text{Br}$	163
NHCONHCl		CS(NHCONHCl)_2	160
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$\text{CCl}_3\text{CH=NC(=S)NHCONHCl}$	160
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$	162		176 (80)
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		<i>Of Sulfonamides</i>	
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$	162	$\text{C}_6\text{H}_5\text{CH}_2\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$\text{C}_6\text{H}_5\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$p\text{-ClC}_6\text{H}_4\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$p\text{-O}_2\text{NC}_6\text{H}_4\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$p\text{-CH}_3\text{OC}_6\text{H}_4\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$o\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$m\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$2,4\text{-(CH}_3)_2\text{C}_6\text{H}_3\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$		$2,4,6\text{-(CH}_3)_3\text{C}_6\text{H}_2\text{SO}_2\text{NHCONHCl}$	159
$\text{NHCH(OC}_2\text{H}_5\text{)}_2\text{CCl}$			159

Note. References 342 to 537 are on pp. 266-269.

TABLE XXIV
ETHERS OF N-METHYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

N-Methylol Ether	References (Yield, %)	N-Methylol Ether	References (Yield, %)
<i>Amides</i>		$(n-C_{11}H_{23}, \text{CONHCH}_2)_2\text{O}$	217 (70), 222
$\text{HCONHCH}_2\text{OCH}_2$	415 (11)	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OCH}_3$	138 (85), 217, 478
$\text{HCONHCH}_2\text{CH}_2\text{O}$	476 (>64)	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5$	138 (84), 217
$\text{CH}_3\text{CONHCH}_2\text{OCH}_2$	415 (90-94)	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5, n$	217 (70)
$\text{CH}_3\text{CONHCH}_2\text{OCH}_2\text{C}_2\text{H}_5$	312	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5, i$	138 (86), 217
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CONHCH}_2\text{OCH}_2$	79	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5, n$	138, 217
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CONHCH}_2\text{OC}_2\text{H}_5$	79	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5, i$	138 (50), 478, 479
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CONHCH}_2\text{OC}_2\text{H}_5, n$	79	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5$	478
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CONHCH}_2\text{OC}_2\text{H}_5, i$	79	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5$	138 (50), 217
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CONHCH}_2\text{OC}_2\text{H}_5$	79	$(n-C_{17}H_{35}, \text{CONHCH}_2)_2\text{O}$	217 (95)
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CONHCH}_2\text{OCH}_2\text{CHCO}_2\text{C}_2\text{H}_5$	79 (27)	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5$	479
NHCOC_2H_5		$n-C_{17}H_{35}, \text{CONHCH}_2\text{OC}_2\text{H}_5$	479
$\text{C}_2\text{H}_5\text{CONHCH}_2\text{CONHCH}_2\text{OCH}_2$	79	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OCH}_2\text{CO}_2\text{H}$	479
$\text{C}_2\text{H}_5\text{CONHCH}_2\text{CONHCH}_2\text{OC}_2\text{H}_5$	79	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OCH}(\text{CH}_3)\text{CO}_2\text{H}$	479
$\text{C}_2\text{H}_5\text{CONHCH}_2\text{CONHCH}_2\text{OCH}_2\text{C}_2\text{H}_5$	79	$n-C_{17}H_{35}, \text{CONHCH}_2\text{OCH}_2\text{PO}(\text{OH})_2$	235
		$(n-C_{11}H_{23}, \text{CONHCH}_2)_2\text{O}$	217 (90)
		$\text{CH}_3=\text{CHCONHCH}_2\text{OCH}_3$	423 (70), 477, 480
	312	$\text{CH}_3=\text{CHCONHCH}_2\text{OC}_2\text{H}_5$	477
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{OC}_2\text{H}_5$	79	$(\text{CH}_3=\text{CHCONHCH}_2)_2\text{O}$	422 (55)
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{OC}_2\text{H}_5, n$	79	$\text{CH}_3=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OCH}_3$	477 (80), 480 (80)
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}_2\text{OCH}_2\text{CHCO}_2\text{C}_2\text{H}_5$	388 (73)	$\text{CH}_3=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OC}_2\text{H}_5$	477
NHCOC_2H_5	79	$\text{CH}_3=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OCH}(\text{CH}_3)_2$	477
$(\text{C}_2\text{H}_5\text{CONHCH}_2)_2\text{O}$	153 (55)	$\text{CH}_3=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OC}_2\text{H}_5$	477
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}(\text{CH}_3)\text{CONHCH}_2\text{OC}_2\text{H}_5$	79	$\text{CH}_3=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OC}_2\text{H}_5$	477
$\text{C}_2\text{H}_5\text{CH}_2\text{CONHCH}(\text{CH}_3)\text{CONHCH}_2\text{OCH}_2\text{C}_2\text{H}_5$	79	$\text{CH}_3=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OC}_2\text{H}_5$	477
$(\text{C}_2\text{H}_5\text{CONHCH}_2)_2\text{O}$	54	$\text{CH}_3=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OC}_2\text{H}_5$	477

Amides (contd.)				
$\text{CH}_2=\text{C}(\text{CH}_2)_n\text{CONHCH}_2\text{O}$ 				
$\text{CH}_2=\text{C}(\text{CH}_2)_n\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	477			
$\text{CH}_2=\text{C}(\text{CH}_2)_n\text{CONHCH}_2\text{OCH}_2\text{C}_6\text{H}_5$	477			
$\text{CH}_2=\text{C}(\text{CH}_2)_n\text{CONHCH}_2\text{O}$	477			
$\text{CH}_2\text{CH}=\text{CH}_2\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	424 (43)			
$\alpha\text{-C}_6\text{H}_4\text{CH}=\text{CH}_2\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	423 (64), 480			
$\text{CHCONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	312			
$\text{CHCONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	423			
$\text{C}_6\text{H}_5\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	79			
$\text{C}_6\text{H}_5\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	478, 479			
$\text{C}_6\text{H}_5\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	96 (54)			
$(\text{C}_6\text{H}_5)_2\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	10, 14 (80), 220 (77)			
$(\text{C}_6\text{H}_5)_2\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	221 (50)			
$(\text{C}_6\text{H}_5)_2\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	430 (43)			
 $\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	430			
 $\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	430			
 $\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	430			
 $\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	430			
 $\text{CONHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$	430			



Note References 382 to 537 are on pp. 266-269.

TABLE XXIV—Continued
ETHERS OF N-METHYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

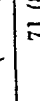
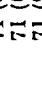
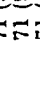
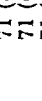

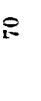
N-Methylol Ether	References (Yield, %)	N-Methylol Ether	References (Yield, %)
<i>Imide</i>			
	188	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$	71 (83) 71 (86) 71 (97) 71 (94) 71 (86) 71 (85) 71 (80)
	66	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OCH}_3$ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OCH}_3$	71 (50)
	85 (17)	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OCH}_3$ $[o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{O}]_2$	70 61, 151, 220, 263 70
	8 (41)	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OCH}_3$ <i>Carbamyl Compounds</i> $\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}_2\text{OCH}_3$ $\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}_2\text{OCH}_3$ $\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}_2\text{OCH}_3$ $(\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}_2\text{O})_2$ $n\text{-C}_{18}\text{H}_{37}\text{O}_2\text{CNHCH}_2\text{OCH}_3\text{CO}_2\text{H}$	218 (95) 218 (82) 218 (96) 153, 218 479
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OCH}_3$	70, 71, 151, 188		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_2\text{H}_5$	70, 71 (92), 104 (good), 151		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_3\text{H}_7$	70		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_4\text{H}_9$	71 (78)		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_6\text{H}_5$	71 (48)		
			73
			73

TABLE XXIV—Continued
ETHERS OF N-METHYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

N-Methylol Ether	References (Yield, %)	N-Methylol Ether	References (Yield, %)
Carbamyl Compounds (contd.) $\begin{array}{c} \text{CH}_3\text{NCH}_2\text{OCH}_3 \\ \diagup \quad \diagdown \\ \text{O} \quad \text{CO} \\ \diagdown \quad \diagup \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \end{array}$	02, 219 (66), 357, 484	$\begin{array}{c} \text{NCH}_2\text{OCH}_3 \\ \\ \text{CO} \\ \\ \text{NCH}_2\text{OCH}_3 \end{array}$	180 (41)
$\begin{array}{c} \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \end{array}$	485 (64)	$\begin{array}{c} \text{NCH}_2\text{OCH}_3 \\ \\ \text{CO} \\ \\ \text{NCH}_2\text{OCH}_3 \end{array}$	180 (82)
$\begin{array}{c} \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \end{array}$	485 (30)	$\begin{array}{c} \text{NCH}_2\text{OCH}_3 \\ \\ \text{CS} \\ \\ \text{NCH}_2\text{OCH}_3 \end{array}$	240, 457
$\begin{array}{c} \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \\ \text{CH}_2\text{NCH}_2\text{OCH}_3 \end{array}$	485	$\begin{array}{c} \text{NCH}_2\text{OCH}_3 \\ \\ \text{CS} \\ \\ \text{NCH}_2\text{OCH}_3 \end{array}$	179 (87)
$\begin{array}{c} \text{HO(CH}_2)_2\text{N} \quad \text{CH}_2\text{NCH}_2\text{OCH}_3 \\ \quad \diagdown \\ \text{CO} \end{array}$	185 (92)	$\begin{array}{c} \text{NCH}_2\text{OCH}_3 \\ \\ \text{CS} \\ \\ \text{NCH}_2\text{OCH}_3 \end{array}$	240
$\begin{array}{c} \text{[CONCH}_2\text{...]} \\ \quad \diagdown \\ \text{CO} \end{array}$			

Note: References 382 to 537 are on pp. 266-269.

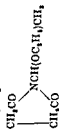
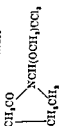
TABLE XXV—Continued
ETHERS OF N- α -ALKYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

ETHERS OF N- α -ALKYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMATES	N- α -Alkylol Ether	Reference (Yield, %)	N- α -Alkylol Ether	Reference (Yield, %)
<i>Aliphatic Amides (contd.)</i>				
C	$n\text{-C}_4\text{H}_9\text{CONHCH(CH}_3\text{)}_2\text{O}$	207	$2\text{-CH}_3\text{O-5-ClC}_6\text{H}_4\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	206
	$n\text{-C}_4\text{H}_9\text{CONHCH(CH}_3\text{)}_2\text{CHBr}_2$	207	$2\text{-CH}_3\text{O-5-ClC}_6\text{H}_4\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	206
	$n\text{-C}_4\text{H}_9\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	160	$(2\text{-CH}_3\text{O-5-ClC}_6\text{H}_4\text{CONHCH(CH}_3\text{)}_2\text{O})$	226
	$n\text{-C}_4\text{H}_9\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	160	$2\text{-CH}_3\text{O-3,5-Cl}_2\text{C}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	206, 226
	$n\text{-C}_4\text{H}_9\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	163	$2\text{-CH}_3\text{O-3,5-Cl}_2\text{C}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	206
<i>Aromatic Amides</i>	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{CHCl}_2$	208	$(2\text{-CH}_3\text{O-3,5-Cl}_2\text{C}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{O})$	226
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{CHCl}_2$	208	$2\text{-CH}_3\text{O-5-BrC}_6\text{H}_4\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	228
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{CHBr}_2$	208	$2\text{-CH}_3\text{O-5-BrC}_6\text{H}_4\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	205
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{CHBr}_2$	95	$(2\text{-CH}_3\text{O-3,5-Br}_2\text{C}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{O})$	228
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{CHBr}_2$	95	$2\text{-CH}_3\text{O-3-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	206, 225
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{O}$	95, 220	$(2\text{-CH}_3\text{O-3-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{O})$	225
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{CHBr}_2$	106	$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	205, 225
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{O}$	160	$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	205
	$\text{C}_6\text{H}_5\text{CONHCH(CH}_3\text{)}_2\text{O}$	231	$(2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{O})$	225
	$2\text{-HO-3,5-Br}_2\text{C}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	228	$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106, 108
$2\text{-HO-3-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	225	$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106	
$2\text{-HO-3,5-Br-3-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	225	$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106	
$2\text{-HO-3,5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	225	$(2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{O})$	108	
$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106	$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106	
$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{O}$	106	$2\text{-CH}_3\text{O-5-O}_2\text{NC}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106	
$2\text{-CH}_3\text{O-3,5-Br}_2\text{C}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	226	$2\text{-CH}_3\text{O-3,5-Br}_2\text{C}_6\text{H}_3\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106	
$2\text{-CH}_3\text{O-5-ClC}_6\text{H}_4\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	206, 226	$2\text{-CH}_3\text{O-5-ClC}_6\text{H}_4\text{CONHCH(CH}_3\text{)}_2\text{CCl}_3$	106	

Aromatic Amides (contd.)



Lactams and Imides



168
106
106
106

168

204 (80)

204 (70)

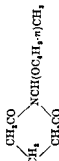
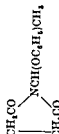
204 (92)

204 (57)

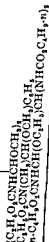
204 (100)

101 (50)

232 (93)



Carbamyl Compounds



232 (95)

232 (79)

232 (91)

232 (82)
232 (41)
214 (63)

73, 95

95
234 (79)
94
94

94, 95,
229, 230
223
223

223
216 (62)
223 (good)

Note: References 382 to 537 are on pp. 266-269.

TABLE XXV.—Continued
ETHERS OF N- α -ALKYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES




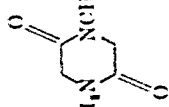



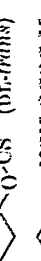



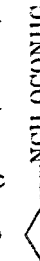
ETHERS OF N- α -ALKYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, CARBAMATES, ETC.	N- α -Alkylol Ether	References (Yield, %)	N- α -Alkylol Ether	References (Yield, %)
Carbamyl Compounds (contd.)				
$\begin{array}{c} \\ \text{6-C}_6\text{H}_4\text{O}_2\text{CNHCHCl}_2\text{O} \\ \text{1-C}_6\text{H}_4\text{O}_2\text{CNHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{2-C}_6\text{H}_4\text{O}_2\text{CNHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{H}_2\text{NCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{H}_2\text{NCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{H}_2\text{NCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{H}_2\text{NCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$		95 73 73 161 161 161 161	$\begin{array}{c} \\ \text{C}_6\text{H}_5\text{NHCONHCHCl}_2\text{O} \\ \text{C}_6\text{H}_5\text{NHCONHCH(OCH}_3\text{)}_2\text{CH}_3 \\ \text{C}_6\text{H}_5\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{C}_6\text{H}_5\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$	163 234 161 161
	$\begin{array}{c} \\ \text{H}_2\text{NCONHCHCl}_2\text{O} \\ \text{H}_2\text{NCONHCH(OCH}_3\text{)}_2\text{CHBr}_2 \\ \text{H}_2\text{NCONHCH(OCH}_3\text{)}_2\text{CHBr}_2 \\ \text{H}_2\text{NCONHCH(OCH}_3\text{)}_2\text{CHBr}_2 \end{array}$	101, 473 162 162 162	$\begin{array}{c} \\ (\text{C}_6\text{H}_5\text{NHCONHCHCl}_2)_2\text{O} \\ \text{p-ClC}_6\text{H}_4\text{NHCONHCH(OCH}_3\text{)}_2\text{CH}_3 \\ \text{m-O}_2\text{NC}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{m-O}_2\text{NC}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$	161 163 163 163
	$\begin{array}{c} \\ (\text{H}_2\text{NCONHCHCl}_2)_2\text{O} \\ \\ (\text{CNHCONHCHCl}_2)_2\text{O} \\ \\ \text{CH}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$	162	$\begin{array}{c} \\ (\text{m-O}_2\text{NC}_6\text{H}_3\text{NHCONHCHCl}_2)_2\text{O} \\ \text{p-O}_2\text{NC}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{p-O}_2\text{NC}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$	227 227 227
	$\begin{array}{c} \\ (\text{CH}_3\text{NHCONHCHCl}_2)_2\text{O} \\ \\ \text{CH}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CHBr}_2 \end{array}$	163 163	$\begin{array}{c} \\ (\text{p-O}_2\text{NC}_6\text{H}_3\text{NHCONHCHCl}_2)_2\text{O} \\ \text{o-CH}_3\text{C}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{o-CH}_3\text{C}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$	227 227 227
	$\begin{array}{c} \\ (\text{CH}_3\text{NHCONHCHCl}_2)_2\text{O} \\ \\ \text{C}_6\text{H}_5\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{C}_6\text{H}_5\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$	163 163 163	$\begin{array}{c} \\ (\text{o-CH}_3\text{C}_6\text{H}_3\text{NHCONHCHCl}_2)_2\text{O} \\ \text{p-CH}_3\text{C}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \\ \text{p-CH}_3\text{C}_6\text{H}_3\text{NHCONHCH(OCH}_3\text{)}_2\text{CCl}_3 \end{array}$	227 227 227

Carbamyl Compounds (contd.)

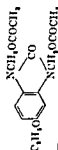
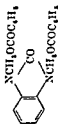
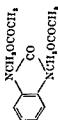
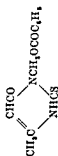
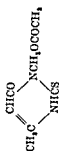
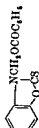
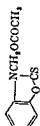
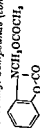
$(p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCONHCHCl}_2)_2\text{O}$ $\text{CH}_3\text{CONHCONHCH}(\text{OCH}_2)_2\text{CCl}_2$ $\text{CH}_3\text{CONHCONHCH}(\text{OC}_2\text{H}_5)_2\text{CCl}_2$	227 161 161	$\text{CCl}_3\text{CH}(\text{OCOC}_2\text{H}_5)_2\text{NHCONHCHCl}_2$ <div>O $\diagup \quad \diagdown$ $\text{CCl}_3\text{CHOHNHCONHCHCl}_2$</div>	160
$(\text{CH}_3\text{CONHCONHCHCl}_2)_3\text{O}$ $\text{CO}[\text{NHCH}(\text{OCH}_3)_2\text{CCl}_2]_3$ $\text{CO}[\text{NHCH}(\text{OC}_2\text{H}_5)_2\text{CCl}_2]_3$ $\text{CO}[\text{NHCH}(\text{OC}_2\text{H}_5)_2\text{CCl}_2]_2$ $\text{CO}[\text{NHCH}(\text{OCH}_3)_2\text{CBr}_2]_2$ $\text{CO}[\text{NHCH}(\text{OC}_2\text{H}_5)_2\text{CBr}_2]_2$	161 161 160, 161 161 162 162	$\text{CH}_3\text{NCH}(\text{OCH}_3)_2\text{CH}_2$ <div>CO $\diagup \quad \diagdown$ CH_3NH</div> $\text{CH}_3\text{NCH}(\text{OC}_2\text{H}_5)_2\text{CH}_2$ <div>CO $\diagup \quad \diagdown$ CH_3NH</div>	224 224
$\text{NHCH}(\text{OCH}_3)_2\text{CCl}_2$ $\text{NHCH}(\text{OC}_2\text{H}_5)_2\text{CBr}_2$ $\text{NHCH}(\text{OC}_2\text{H}_5)_2\text{CCl}_2$	162 162	$\text{CH}_3\text{NCH}(\text{OCH}_3)_2\text{CH}_2$ <div>CO $\diagup \quad \diagdown$ CH_3NH</div> $\text{CH}_3\text{NCH}(\text{OCH}_3)_2\text{CH}_2$ <div>CO $\diagup \quad \diagdown$ CH_3NH</div>	224 224
$\text{NHCH}(\text{OCH}_3)_2\text{CBr}_2$ $\text{NHCH}(\text{OC}_2\text{H}_5)_2\text{CCl}_2$	162 162	$\text{CH}_3\text{NCH}(\text{OC}_2\text{H}_5)_2\text{CH}_2$ <div>CO $\diagup \quad \diagdown$ CH_3NH</div> $\text{CH}_3\text{NCH}(\text{OC}_2\text{H}_5)_2\text{CH}_2$ <div>CO $\diagup \quad \diagdown$ CH_3NH</div>	224 224
$\text{NHCH}(\text{OC}_2\text{H}_5)_2\text{CBr}_2$	162	$\text{CH}_3\text{NCH}(\text{OC}_2\text{H}_5)_2\text{CH}_2$ <div>CO $\diagup \quad \diagdown$ CH_3NH</div>	224
$[\text{CCl}_3\text{CH}(\text{OCOC}_2\text{H}_5)_2\text{NHCONHCHCl}_2]_3\text{O}$	160	<i>Sulfonamides</i> $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{N}(\text{CH}_3)_2\text{CH}(\text{OC}_2\text{H}_5)_2\text{CH}_2$	232 (84)

Note: References 382 to 537 are on pp. 266-269.

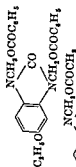
TABLE XXVI
ESTERS OF N-METHYLOL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS

N-Methylol Ester	References (Yield, %)	N-Methylol Ester	References (Yield, %)
<i>Amides and Lactams</i>			
$\text{CH}_3\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	244 (21)		8 (34)
$\text{C}_6\text{H}_5\text{CH}_2\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	70 (60)		
$\text{C}_6\text{H}_5(\text{CH}_2)_2\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	70		
$n\text{-C}_4\text{H}_9\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	222		
$n\text{-C}_6\text{H}_{13}\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	138 (66), 236		
$n\text{-C}_{11}\text{H}_{23}\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	235		
$\text{CH}_3\text{C}(\text{CH}_3)_2\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	477 (61)		
$\text{CH}_3\text{C}(\text{CH}_3)_2\text{CON}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	477		
	242		8 (66)
$\text{C}_6\text{H}_5\text{CO}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{OCOCCH}_3)_2$	65 (50)		8 (21)
<i>Imides</i>			
			220 (24) 243
	66 (76)		181 (65)
			181 (55)
	8 (93)		181 (65)

Carbamyl Compounds (contd.)

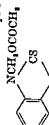


194 (75)



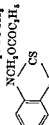
237

178 (56)



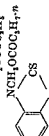
238

178 (56)



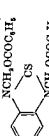
240

239



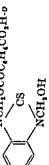
240, 457

239



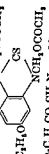
238

238



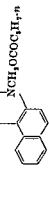
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238



237

237



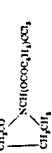
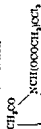
241

Note References 382 to 537 are on pp. 266-269.

Aromatic Amides (contd.)

[illegible]

Lactams and Imides



Carbamyl Compounds

$\text{C}_6\text{H}_5\text{O}_2\text{CNHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	94 (80)
$\text{CCl}_3\text{CH}=\text{NCSNHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	160
$\text{CO}_2\text{NHCH}(\text{OCOCCH}_3)_2\text{CCl}_{1.5}$	161
$\text{CO}_2\text{NHCH}(\text{OCOCCH}_3)_2\text{CB}_{1.5}\text{I}_2$	162
$\text{CH}_2\text{CONHCH}(\text{OCOCCH}_3)_2\text{CB}_{1.5}$	161
$\text{CH}_2\text{CONHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	163
$\text{CH}_2\text{CON}(\text{CH}_3)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	163
$\text{CH}_2\text{CON}(\text{C}_6\text{H}_5)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CB}_{1.5}$	163
$\text{CH}_2\text{CON}(\text{C}_6\text{H}_5)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	163
$\text{CH}_2\text{CON}(\text{C}_6\text{H}_5)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CB}_{1.5}$	163
$\text{CH}_2\text{CON}(\text{C}_6\text{H}_5\text{NO}_2\text{-}m)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	227
$\text{CH}_2\text{CON}(\text{C}_6\text{H}_5\text{NO}_2\text{-}p)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	227
$\text{CH}_2\text{CON}(\text{C}_6\text{H}_5\text{CH}_2\text{-}o)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	227
$\text{CH}_2\text{CON}(\text{C}_6\text{H}_5\text{CH}_2\text{-}p)\text{CONHCH}(\text{OCOCCH}_3)_2\text{CCl}_2$	227

Sulfonamides

$C_6H_5CH_2SO_2NHCH(OCOCCH_3)CCl_2$	159
$C_6H_5SO_2NHCH(OCOCCH_3)CCl_2$	159
$p\text{-ClC}_6H_4SO_2NHCH(OCOCCH_3)CCl_2$	159
$p\text{-O}_2NC_6H_4SO_2NHCH(OCOCCH_3)CCl_2$	159
$p\text{-Cl}_2C_6H_3SO_2NHCH(OCOCCH_3)CCl_2$	159
$o\text{-CH}_3C_6H_4SO_2NHCH(OCOCCH_3)CCl_2$	159
$m\text{-CH}_3C_6H_4SO_2NHCH(OCOCCH_3)CCl_2$	159
$p\text{-CH}_3C_6H_4SO_2NHCH(OCOCCH_3)CCl_2$	159
$2,4\text{-(CH}_3)_2C_6H_3SO_2NHCH(OCOCCH_3)CCl_2$	159
$2,4,6\text{-(CH}_3)_3C_6H_2SO_2NHCH(OCOCCH_3)CCl_2$	159
 $SO_2NHCH(OCOCCH_3)CCl_2$	159



Note: References 392 to 537 are on pp. 260-269.

TABLE XXVIII
N-HALOMETHYL AND N- α -HALOALKYL DERIVATIVES OF AMIDES, LACTAMS,
IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $RCON(R')CH(R'')OH \rightarrow RCON(R')CH(R'')X$



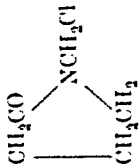
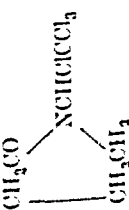
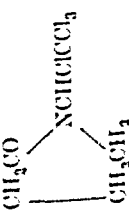
N- α -Halomethyl Derivatives	Method*	References (Yield, %)
<i>Amides</i>		
$HCONHCH_2Cl$	PCl_5 , dioxane	96
$HCONHCH_2CCl_3$	PCl_5 , $(C_2H_5)_2O$	101 (76)
	PCl_5 , heat	160
	PCl_5 , heat	207
$HCONHCH_2CBr_3$	PCl_5 , dioxane	96
$CH_3CONHCH_2Cl$	CH_3CONH_2 , $(CH_3O)_2$, HCl , CH_3CO_2H	202 (60), 203 (60)
	CH_3CONH_2 , $(CH_3O)_2$, HCl , dioxane	201
	PCl_5 , dioxane	96
$CH_3CONHCH_2Br$	CH_3CONH_2 , CH_3CHO , HCl , dioxane	201
$CH_3CONHCH_2CH_3$	PCl_5 , heat	209
$CH_3CONHCH_2CCl_3$	$CH_3CONHCH=CCl_2$, Cl_2 , $CHCl_3$	209
	PCl_5 , heat	207
$CH_3CONHCH_2CBr_3$	CH_3CONH_2 , $n-C_3H_7CHO$, HCl , dioxane	201
$CH_3CONHCH_2(CH_2)_3CH_3$	PCl_5 , dioxane, 30–40°	32
$CH_3CON(CH_3)CH_2Cl$	PCl_5 , dioxane, 30–40°	32 (good)
$CH_3CON(C_3H_7-n)CH_2Cl$	PCl_5 , dioxane, 30–40°	32
$CH_3CON(C_3H_7-i)CH_2Cl$	PCl_5 , dioxane, 30–40°	196
$CH_3CON(CH_2C_6H_4)CH_2Cl$	CH_3CONHR , $(CH_3O)_2$, HCl , C_6H_6	216
$CH_3CON(C_{11}H_{23-n})CH_2Cl$	CH_3COCl , $CH_3N=CHC_6H_5$	96
$CH_3CON(CH_3)CHClC_6H_5$	PCl_5 , $(C_2H_5)_2O$ /dioxane	207
$CH_3CONHCH_2Cl$	PCl_5 , heat	100, 186 (76)
$CH_3CONHCH_2CBr_3$	PCl_5 , $(C_2H_5)_2O$	96
$CCl_3CONHCH_2Cl$	PCl_5 , dioxane	
$C_3H_5CONHCH_2Cl$		

$C_2H_5CONHCH_2Br$	PBr_3 , dioxane	96
$C_2H_5CONHCHClCB_r_3$	PCl_5 , heat	207
$n-C_3H_7CONHCHClCB_r_3$	PCl_5 , heat	207
$n-C_{11}H_{23}CON(C_6H_{11-cyclo})CH_2Cl$	$RCONHR'$, $(CH_2O)_2$, HCl , C_6H_6	196
$n-C_{17}H_{35}CONHCH_2Cl$	$RCONH_2$, $(CH_2O)_2$, HCl , CH_2Cl_2	195
	$RCONH_2$, $(CH_2O)_2$, HCl , C_6H_6	200
$n-C_{17}H_{35}CON(CH_3)CH_2Cl$	$RCONHCH_3$, $(CH_2O)_2$, HCl , C_6H_6	196
$n-C_{17}H_{35}CON(CH_2)CH_2Br$	$RCONHCH_3$, $(CH_2O)_2$, HBr , C_6H_6	196
$n-C_{17}H_{35}CONCH_2Cl$		
$\begin{array}{c} CH_3 \\ \diagup \quad \diagdown \\ n-C_{17}H_{35}CONCH_2Cl \\ n-C_{21}H_{43}CONHCH_2Cl \\ C_6H_5CONHCH_2Cl \end{array}$	$(RCONH)_2CH_2$, $(CH_2O)_2$, HCl , C_6H_6	198, 199
$C_6H_5CONHCH_2Br$	$RCONH_2$, $(CH_2O)_2$, HCl , C_6H_6	197
$C_6H_5CONHCHClCH_2Cl$	PCl_5 , $(C_2H_5)_2O$	96 (78), 100
$C_6H_5CONHCHBrCHCl_2$	$C_6H_5CONH_2$, $(CH_2O)_2$, HCl , CH_3CO_2H	202 (62)
$C_6H_5CONHCHClCl_3$	PBr_5 , $(C_2H_5)_2O$	96 (80)
$C_6H_5CON(CH_3)CH_2Cl$	$C_6H_5CONHCH=CCl_2$, HCl	208
$C_6H_5CON(CH_3)CHClC_6H_5$	$C_6H_5CONHCH=CCl_2$, HBr	208
$2,4-Cl_2C_6H_3CONHCH_2Cl$	PCl_5 , $(C_2H_5)_2O$ /dioxane	101 (72)
$2-CH_3O-5-ClC_6H_3CONHCHClCl_3$	PCl_5 , dioxane, 30–40°	32
$2-CH_3O-3-ClC_6H_3CONHCHClCl_3$	C_6H_5COCl , $CH_3N=CHC_6H_5$	216 (55)
$2-CH_3O-5-BrC_6H_3CONHCHClCl_3$	PCl_5 , dioxane	96
$2-CH_3O-5-BrC_6H_3CONHCHBrCl_3$	PCl_5 , heat	206 (94)
$2-CH_3O-3,5-Br_2C_6H_3CONHCHClCl_3$	PCl_6 , heat	206
$2-CH_3O-5-NC_6H_3CONHCHClCl_3$	PCl_5 , heat	205
$o-CH_3C_6H_4CONHCHClCl_3$	PCl_5 , heat	205
	PCl_5 , heat	205
	PCl_5 , heat	106

Note: References 382 to 537 are on pp. 266–269.

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

TABLE XXVIII—Continued
 N-HALOMETHYL AND N- α -HALOALKYL DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $RCON(R')CH(R'')OH \rightarrow RCON(R')CH(R'')X$

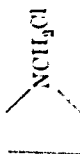
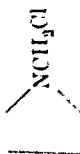

N- α -Halomethyl Derivatives	Method*	References (Yield, %)
<i>Amides (contd.)</i>		
<i>m</i> -CH ₃ C ₆ H ₄ CONHCHClCCl ₃	PCl ₅ , heat	106
<i>p</i> -CH ₃ C ₆ H ₄ CONHCHClCCl ₃	PCl ₅ , heat	106
C ₂ H ₅ O ₂ CNHCHClCCl ₃	PCl ₅ , heat	160
C ₂ H ₅ O ₂ CNHCHBrCCl ₃	PBr ₅ , heat	160
(CONHCHClCCl ₃) ₂	PCl ₅ , heat	163
	PCl ₅ , heat	204
	PCl ₅ , heat	204
<i>Lactams</i>		
	SOCl ₂	177 (85), 184 (87)
	PCl ₅ , (C ₂ H ₅) ₂ O/dioxano	33
	PCl ₅ , (C ₂ H ₅) ₂ O/dioxano	101 (99)


	SOCl ₂ , C ₆ H ₆	184 (70)
	PCl ₅ , (C ₂ H ₅) ₂ O/dioxane	33
	PCl ₅ , CH ₃ COCl, CCl ₄	1, 65 (91)
	PCl ₅ , CHCl ₃	66 (75)
	PBr ₃ , C ₆ H ₆	188 (91)
	PBr ₃ , CHCl ₃	66
	N-Chloromethylmaleimido, HCl	8

Note: References 382 to 537 are on pp. 268-269.

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

TABLE XXVIII—Continued
 N-HALOMETHYL AND N- α -HALOALKYL DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $\text{RCON(R')CH(R'')OH} \rightarrow \text{RCON(R')CH(R'')X}$

N- α -Halomethyl Derivatives	Method*	References (Yield, %)
<i>Imides (contd.)</i>    $\alpha\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{Cl}$	$\text{PCl}_3, (\text{CH}_3)_3\text{CO}$ $\text{PBr}_3, (\text{CH}_3)_3\text{CO}$ $\text{PCl}_5, (\text{C}_2\text{H}_5)_2\text{O}$ $\alpha\text{-C}_6\text{H}_4(\text{CO})_2\text{NH}, (\text{CH}_3\text{O})_3\text{N}, \text{HCl},$ $\text{CH}_3\text{CO}_2\text{H}$ Conc'd. HCl , heat $\alpha\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{COCl}$, heat ($-\text{CO}$) $\alpha\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OC}_2\text{H}_5, \text{CH}_3\text{COCl}$ $\alpha\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{CH}_2 \\ \diagdown \quad \diagup \end{array}, \text{CH}_3\text{COCl}$	8 (81) 8 (52) 97 (82) 202 (70) 192, 193 192 190 (90) 191 (81)

$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{Br}$	$\text{PBr}_3, \text{C}_6\text{H}_6$	188 (82)
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_3, \text{Br}_2, 170^\circ$	151 (100)
	Concd. HBr , heat	104 (69), 192, 193
	Concd. $\text{HBr}, \text{H}_2\text{SO}_4$, heat	70 (65)
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{CH}_3\text{COBr} \end{array}$	191 (86)
	Concd. HI , heat	192, 193
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}=\text{CH}_2, \text{HCl}, \text{CHCl}_3$	211 (97)
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{CH}_2\text{Br}, \text{NBS}^\dagger$	214 (89)
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}=\text{CH}_2, \text{Br}_2$	210
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}=\text{CHCH}_3, \text{Br}_2$	212
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}(\text{CO}_2\text{H})\text{CH}_2\text{CH}_3, \text{Br}_2, \text{P}$	212, 215 (52)
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NC}(\text{CH}_3)=\text{CH}_2, \text{Br}_2$	213
	$\text{PCl}_5, (\text{C}_2\text{H}_5)_2\text{O}$	99 (65)
	$\text{SOCl}_2, (\text{C}_2\text{H}_5)_2\text{O}$	182 (54)
	$\text{OCNCH}_2\text{OH}, \text{SOCl}_2$	73 (68)
	$\text{OCNCHOHCCl}_3, \text{SOCl}_2$	73
	$\text{OCNCHClCCl}_3, \text{CH}_3\text{OH}$	73
	$\text{RO}_2\text{CNH}_2, (\text{CH}_2\text{O})_x, \text{HCl}, \text{C}_6\text{H}_6$	197
	$\text{CH}_3\text{O}_2\text{CNHR}, (\text{CH}_2\text{O})_x, \text{HCl}, \text{C}_6\text{H}_6$	196
	$\text{CH}_3\text{O}_2\text{CNHR}, (\text{CH}_2\text{O})_x, \text{HCl}, \text{C}_6\text{H}_6$	196
	$\text{CH}_3\text{O}_2\text{CNHR}, (\text{CH}_2\text{O})_x, \text{HCl}, \text{C}_6\text{H}_6$	190
	$\text{C}_2\text{H}_5\text{O}_2\text{CCl}, \text{CH}_3\text{N}=\text{CHC}_6\text{H}_5$	216
	$\text{OCNCHClCCl}_3, 2,4\text{-Cl}_2\text{C}_6\text{H}_3\text{OH}$	73
	$\text{OCNCHClCCl}_3, 1\text{-C}_{10}\text{H}_7\text{OH}$	73
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{I}$		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCHClCH}_3$		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCHBrCH}_2\text{Br}$		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCHBrCHBrCH}_3$		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCHBrCHBrCH}_3$		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCHBr}(\text{CH}_2)_2\text{Br}$		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NC}(\text{CH}_3)\text{BrCH}_2\text{Br}$		
		

Carbamyl Compounds

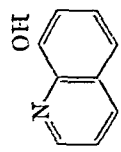
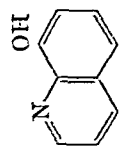
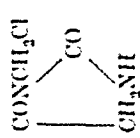
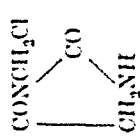
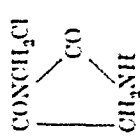
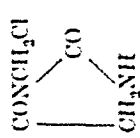
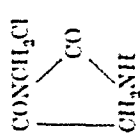
$\text{ClCONHCH}_2\text{Cl}$
ClCONHCHClCCl_3
$\text{CH}_3\text{OCONHCHClCCl}_3$
$n\text{-C}_{22}\text{H}_{45}\text{OCONHCH}_2\text{Cl}$
$\text{CH}_3\text{O}_2\text{CN}(\text{C}_6\text{H}_5)_n\text{CH}_2\text{Cl}$
$\text{CH}_3\text{O}_2\text{CN}(\text{C}_{11}\text{H}_{23-n})\text{CH}_2\text{Cl}$
$\text{CH}_3\text{O}_2\text{CN}(\text{C}_{17}\text{H}_{35-n})\text{CH}_2\text{Cl}$
$\text{C}_2\text{H}_5\text{O}_2\text{CN}(\text{CH}_3)\text{CHClC}_6\text{H}_5$
$2,4\text{-Cl}_2\text{C}_6\text{H}_3\text{O}_2\text{CNHCHClCCl}_3$
$1\text{-C}_{10}\text{H}_7\text{O}_2\text{CNHCHClCCl}_3$


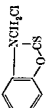
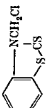
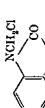
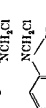
Note. References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

† N-Bromosuccinimide.

TABLE XXVIII—Continued
 N-HALOMETHYL AND N- α -HALOALKYL DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $\text{RCON(R')CH(R'')OH} \rightarrow \text{RCON(R')CH(R'')X}$

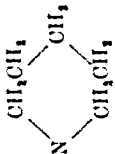
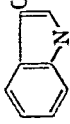
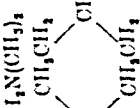


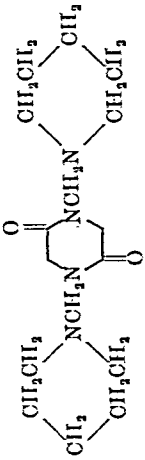
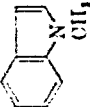
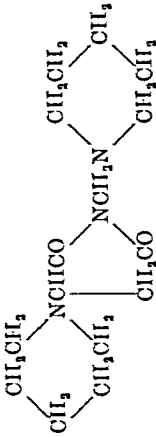
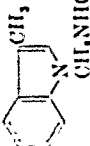

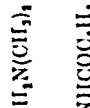

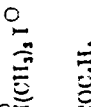

N- α -Halomethyl Derivatives	Method*	References (Yield, %)
<i>Carbamyl Compounds (contd.)</i>		
$2\text{-C}_{10}\text{H}_7\text{O}_2\text{CNHCHClCCl}_3$ 	OCNCHClCCl_3 , $2\text{-C}_{10}\text{H}_7\text{OH}$	73
$\text{O}_2\text{CNHCHClCCl}_3$ 	OCNCHClCCl_3	73
$\text{CS}(\text{NHCHClCCl}_3)_2$ 	PCl_5 , heat	100
CONCH_2Cl 	PCl_5 , heat or concd. HCl	185 (65)
$\text{CO} \cdots \text{NCH}_2\text{Cl}$ 		
$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)\text{NH}$ 	PCl_5 , CHCl_3	187 (60)
 (m.-trans)	SOCl_2 , $(\text{C}_2\text{H}_5)_2\text{O}$	181 (53)

	Concd. HCl, heat	194 (91)
	SOCl ₂	178 (60)
	SOCl ₂ , CHCl ₃	183 (55)
	PCl ₃ , heat	189
	SOCl ₂	180 (59)
	SOCl ₂ , heat	179 (55)
<i>Sulfonamides</i> $\text{C}_6\text{H}_5\text{SO}_2\text{NHCH}_2\text{Cl}$ $\text{C}_6\text{H}_5\text{SO}_2\text{NHCH}(\text{CH}_3)_2$ $\text{C}_6\text{H}_5\text{SO}_2\text{NHCH}(\text{CH}_3)_2\text{CH}_3$	$\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$, (CH ₂ O) ₂ , HCl, dioxane $\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$, CH ₃ CHO, HCl, dioxane $\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$, <i>n</i> -C ₃ H ₇ CHO, HCl, dioxane	201 201 201

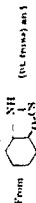
Note. References 382 to 537 are on pp. 266-269.

* Unless otherwise indicated, the N-α-hydroxyalkyl derivative is an unnamed reactant.

TABLE XXIX
N-AMINOMETHYL DERIVATIVES OF AMIDES, LACTAMS, IMIDES, AND CARBAMYL COMPOUNDS*
 $RCONH_2 + CH_2O + R'_2NH \rightarrow RCONHCH_2R'_2$

N-Aminomethyl Derivative	References (Yield, %)	N-Aminomethyl Derivative	References (Yield, %)
	388 (78)		83
	477		426
	96 (72)		65 (65)
	83 (57)		8 (49)
	83 (74)		
	83	From α -methylacrylamido and Dimethylamino	477
		Di-n-propylamino	477
		Di-n-butylamino	477 (75)
	83	Morpholine	477
		$HN(CH_2CH_2OH)_2$	477


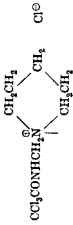
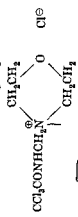


From succinimide and Dimethylamine	186 (75)	Diethylamine	182 (57)
Piperidine	68, 148	Di-n-propylamine	182 (59)
Morpholine	186 (60)	Di-n-butylamine	182 (61)
From maleimide and Diethylamine	432	Morpholine	182 (61)
Di-n-butylamine	8 (74), 432		
Piperidine	8 (82), 432		
Aniline	8 (88), 432		
From phthalimide and Dimethylamine	1 (42), 412		
Piperidine	188		
Aniline	434		
From 3-(and 4-)Nitrophthalimide and Aniline	436		
o-Chloroaniline	436		
m-Chloroaniline	436		
p-Chloroaniline	436		
2,4-Dichloroaniline	436		
o-Bromoaniline	436		
m-Bromoaniline	436		
p-Bromoaniline	436		
o-Nitroaniline	436		
m-Nitroaniline	436		
p-Nitroaniline	436		
2-Chloro-2-nitroaniline	436		
2-Chloro-4-nitroaniline	436		
o-Anisidine	436		
p-Anisidine	436		
o-Toluidine	436		
m-Toluidine	436		
p-Toluidine	436		
2-Naphthylamine	436		
From saccharin and Dimethylamine	182 (12)		



Note. References 382 to 431 are on pp. 268-269.

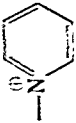
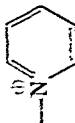
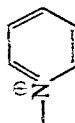
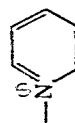
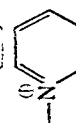
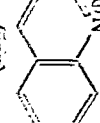
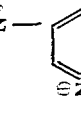

* For an exhaustive compilation of compounds of this class through 1958 see ref. 3





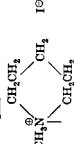
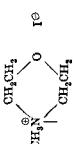


TABLE XXX
N-QUATERNARY AMINOMETHYL DERIVATIVES OF AMIDES, IMIDES, AND CARBAMYL COMPOUNDS

$RCONHCH_2-$	$RCONHCH_2-N^+-X^-$	References (Yield, %)
$CH_3CONHCH_2-$		140
$CCl_3CONHCH_2-$		191 (83)
$C_2H_5CONHCH_2-$		191 (87)
$n-C_{11}H_{23}CONHCH_2-$		140
		140

Note: References 382 to 537 are on pp. 260-269.

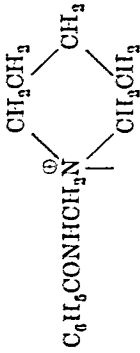
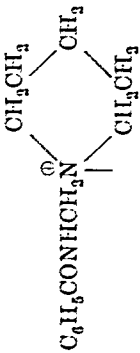
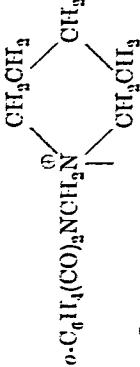
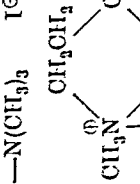
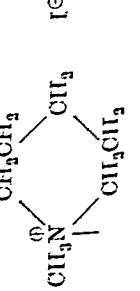
TABLE XXX—Continued
N-QUATERNARY AMINOMETHYL DERIVATIVES OF AMIDES, IMIDES, AND CARBAMYL COMPOUNDS

$\text{RCONHCH}_2\text{—}$	$\text{RCONHCH}_2\text{—N}^+(\text{CH}_3)_2\text{—N}^+(\text{CH}_3)_2\text{—N}^+(\text{CH}_3)_2\text{—}$	References (Yield, %)
$n\text{-C}_{17}\text{H}_{35}\text{CONHCH}_2\text{—}$	      	<p>138 (78), 140, 200, 243</p> <p>140</p> <p>140, 306</p> <p>140</p> <p>140</p> <p>140</p> <p>235</p>
$n\text{-C}_{21}\text{H}_{43}\text{CONHCH}_2\text{—}$		

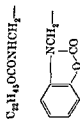
$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CONHCH}_2-$		Cl^-	140
$\left[n\text{-C}_{18}\text{H}_{33}\text{CONCH}_2- \right]$		Cl^-	305
$\left[n\text{-C}_{17}\text{H}_{33}\text{CONCH}_2- \right]$	$\text{N}^+(\text{CH}_3)_3$	Cl^-	199
$\left[n\text{-C}_{19}\text{H}_{33}\text{CONCH}_2- \right]$	$\text{N}^+(\text{C}_2\text{H}_5)_3$	Cl^-	199
$\left[n\text{-C}_{17}\text{H}_{33}\text{CONCH}_2- \right]$		Cl^-	199
		I^-	304 (92)
		I^-	304 (84)
$\text{C}_6\text{H}_5\text{CONHCH}_2-$		Cl^-	66
		Cl^-	191 (94)

Note: References 382 to 537 are on pp. 266-269.

TABLE XXX—Continued
N-QUATERNARY AMINOMETHYL DERIVATIVES OF AMIDES, IMIDES, AND CARBAMYL COMPOUNDS

$\text{RCONHCH}_2\text{—}$	$\text{RCONHCH}_2\text{—N}^+(\text{X}^-)\text{—}$	References (Yield, %)
$\text{C}_6\text{H}_5\text{CONHCH}_2\text{—}$		191 (91)
$\text{C}_6\text{H}_5\text{CONHCH}_2\text{—}$		191 (49)
$\text{o-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{—}$		191 (83)
$\text{o-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{—}$		1, 304 (73)
$\text{o-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{—}$		304 (96)

	304 (87)
	243 (good)
	191 (73)
	235
	194 (90)
	194 (72)
	194 (75)
	194 (74)
	194 (80)



Note. References 382 to 537 are on pp. 266-268.

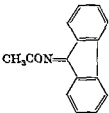
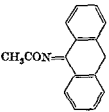
TABLE XXX—Continued
N-QUATERNARY AMINOMETHYL DERIVATIVES OF AMIDES, IMIDES, AND CARBANYL COMPOUNDS

RCONHCH ₃ —	RCONHCH ₃ —N [⊕] — X [⊖]	References (Yield, %)
	$\text{—N}^{\oplus}(\text{CH}_3)_3 \text{ I}^{\ominus}$	180 (34)
		180 (33)
		180 (27)
	$\text{—N}^{\oplus}(\text{CH}_3)_3 \text{ I}^{\ominus}$	179 (88)

Note: References 382 to 537 are on pp. 200–209.

TABLE XXXI

N-ACYL- AND N-SULFONYL-IMINES

Imine Derivative	References (Yield, %)
<i>Amides</i>	
$\text{HCON}=\text{CHC}_6\text{H}_4\text{OH}-p$	297 (60)
$\text{CH}_3\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-p$	297 (90)
$\text{CH}_3\text{CON}=\text{C}(\text{C}_6\text{H}_5)_2$	231 (70)
$\text{CH}_3\text{CON}=\text{C}[\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2-p]_2$	231, 490 (77)
$\text{CH}_3\text{CON}=\text{C}(\text{C}_{10}\text{H}_7-1)\text{C}_6\text{H}_5$	231
$\text{CH}_3\text{CON}=\text{C}(\text{C}_{10}\text{H}_7-2)\text{C}_6\text{H}_5$	231
$\text{CH}_3\text{CON}=\text{C}(\text{C}_{10}\text{H}_7-1)_2$	231
	231
	231, 491 (59), 492
$\text{CH}_2\text{ClCON}=\text{CHCCl}_3$	307
$\text{CH}_2\text{ClCON}=\text{CHCCl}_3$	307
$\text{CH}_2\text{ClCON}=\text{C}(\text{C}_6\text{H}_5)_2$	231
$\text{C}_6\text{H}_5\text{CH}_2\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-o$	299
$\text{C}_6\text{H}_5\text{CH}_2\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-m$	298 (40)
$\text{C}_6\text{H}_5\text{CH}_2\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-p$	297 (80)
$\text{C}_2\text{H}_5\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-o$	299
$\text{C}_2\text{H}_5\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-m$	298 (27)
$\text{C}_2\text{H}_5\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-p$	297 (83)
$\text{C}_2\text{H}_5\text{CON}=\text{C}(\text{C}_6\text{H}_5)_2$	231 (71)
$\text{C}_2\text{H}_5\text{CON}=\text{C}(\text{C}_6\text{H}_5)\text{C}_6\text{H}_4\text{CH}_3-o$	231
$n\text{-C}_8\text{H}_{17}\text{CON}=\text{C}(\text{C}_6\text{H}_5)_2$	231 (65)
$n\text{-C}_8\text{H}_{17}\text{CON}=\text{CHC}_6\text{H}_4\text{OH}-2\text{-Cl}-5$	271

Note: References 382 to 537 are on pp. 266-269.


TABLE XXXII
 SYMMETRICAL N,N'-METHYLENE-*bis* DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N,N'-Methylene- <i>bis</i> Derivative	Method	References (Yield, %)
<i>Amides</i>		
$(\text{HCONH})_2\text{CH}_2$	Amide, $(\text{CH}_3\text{O})_3$ Amide, formalin, $(\text{CH}_3\text{CO})_2\text{O}$ Amide, hexamine	154 (32), 202, 404 281 (21) 495 (53-83)
$(\text{CH}_3\text{CONH})_2\text{CH}_2$	Amide, formalin, $(\text{CH}_3\text{CO})_2\text{O}$ Amido, formalin, $\text{CH}_3\text{CO}_2\text{H}$ Amido, formalin, acid	281 (76) 154 (16), 279 (54) 246, 465
	Amido, $(\text{CH}_3\text{O})_3$ Amido, $(\text{CH}_3\text{O})_x$	494 (good) 250 (62)
	Amide, hexamine, base RCN , CH_3O , HCl , H_2O , 300° RCN , 33% CH_3O , concd. HCl	495 (good) 406
$(\text{CH}_3\text{ClCONH})_2\text{CH}_2$ $(\text{CHCl}_2\text{CONH})_2\text{CH}_2$ $(\text{CCl}_3\text{CONH})_2\text{CH}_2$	$\text{RCONHCH}_2\text{OH}$, acid Amide, $\text{RCONHCH}_2\text{OH}$, acid Amido, $\text{RCONHCH}_2\text{OH}$, acid $\text{RCONHCH}_2\text{OH}$, acid	497 11 (95), 465 465 264
$(\text{CH}_2\text{BrCONH})_2\text{CH}_2$ $(\text{CH}_2\text{ICONH})_2\text{CH}_2$ $(\text{NCSCH}_2\text{CONH})_2\text{CH}_2$ $[(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CONH}]_2\text{CH}_2$ $(\text{C}_6\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CONH})_2\text{CH}_2$	Amide, $\text{RCONHCH}_2\text{OH}$, acid $\text{RCONHCH}_2\text{OH}$, acid $(\text{CH}_3\text{ClCONH})_2\text{CH}_2$, KSCN , $\text{C}_2\text{H}_5\text{OH}$ $\text{RCONHCH}_2\text{OH}$, acid $\text{RCONHCH}_2\text{OH}$, acid $\text{RCONHCH}_2\text{OH}$, acid Amido, formalin, acid $\text{RCONHCH}_2\text{OH}$, acid Amido, formalin, acid	264 (95), 465 465 11, 465 465 153, 465 79 79 79 79 79
$(\text{C}_6\text{H}_5\text{CONHCH}_2\text{CONH})_2\text{CH}_2$		

$(\text{CH}_2=\text{CHCH}_2\text{CONH})_2\text{CH}_2$	4 (18)
$(\text{CH}_2\text{CH}=\text{CHCH}_2\text{CONH})_2\text{CH}_2$	4 (9)
$(\text{C}_6\text{H}_5\text{CH}_2\text{CONH})_2\text{CH}_2$	388 (88)
	79
$(\text{C}_2\text{H}_5\text{O}_2\text{CCH}_2\text{CONH})_2\text{CH}_2$	4 (30), 261
$(\text{H}_2\text{NCOCH}_2\text{CONH})_2\text{CH}_2$	4 (5)
$(\text{NCCH}_2\text{CONH})_2\text{CH}_2$	495 (83)
$(\text{C}_2\text{H}_5\text{CONH})_2\text{CH}_2$	465
	153 (79)
	153 (low)
	153 (40)
	153 (75)
	465
	497
	465, 498
	499 (79)
	499 (91)
	500
	253 (55)
	500
	79
	79
	79
	501
	502
	4 (40)
	253 (94)
	253 (40)
	253 (86)
$\text{RCN}, (\text{CH}_2\text{O})_x, 75\% \text{H}_2\text{SO}_4$	
$\text{RCN}, (\text{CH}_2\text{O})_x, 90\% \text{H}_2\text{SO}_4$	
Amide, formalin, acid	
$\text{RCONHCH}_2\text{OR}', \text{acid}$	
$\text{RCN}, (\text{CH}_2\text{O})_x, \text{concd. H}_2\text{SO}_4$	
$\text{RCN}, (\text{CH}_2\text{O})_x, \text{C}_6\text{H}_{12}, \text{H}_2\text{SO}_4$	
Amide, hexamine, $\text{HCON}(\text{CH}_3)_2$, heat	
Amide, formaldehyde, acid	
Amide, $\text{RCONHCH}_2\text{OH}$, acid	
$\text{RCONHCH}_2\text{OH}$, heat	
$\text{RCONHCH}_2\text{OH}$, acid	
Amide, formalin, acid	
Amide, formaldehyde, acid	
$\text{RCN}, 33\% \text{CH}_2\text{O}$, concd. HCl	
$\text{CH}_2=\text{CHCN}, \text{CH}_2\text{O}, \text{HCl}, \text{H}_2\text{O}, 400^\circ$	
$\text{RCN}, 37\% \text{CH}_2\text{O}$, concd. H_2SO_4	
Amide, $(\text{CH}_2\text{O})_x, \text{HCl}$	
$\text{RCN}, 53\% \text{CH}_2\text{O}, \text{HCl}, 300^\circ$	
$\text{RCONHCH}_2\text{OH}$, acid	
$\text{RCN}, 35\% \text{CH}_2\text{O}, \text{HCl}, 380^\circ$	
$\text{RCONHCH}_2\text{OH}$, acid	
Amide, formalin, acid	
$\text{RCONHCH}_2\text{OH}$, acid	
Amide, $(\text{CH}_2\text{O})_x$, acid	
Amide, hexamine, heat	
$\text{RCN}, (\text{CH}_2\text{O})_x, 85\% \text{H}_2\text{SO}_4$	
$\text{RCONHCH}_2\text{OH}, \text{HBr}$ or H_2SO_4	
$\text{CH}_2=\text{C}(\text{CH}_3)\text{CONHCH}_2\text{OH}, \text{Br}_2$	
$\text{CH}_2\text{BrCBr}(\text{CH}_3)\text{CONHCH}_2\text{OH}, \text{Br}_2$	

Note: References 382 to 537 are on pp. 266-269.

TABLE XXXII—Continued
 SYMMETRICAL N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
<i>Amides* (contd.)</i>		
$(n\text{-C}_4\text{H}_9\text{CONH})_2\text{CH}_2$	Amide, $\text{RCONHCH}_2\text{OH}$, acid $\text{RCONHCH}_2\text{OH}$, heat	419 (85) 419 (73)
$[(\text{C}_2\text{H}_5)_2\text{CHCONH}]_2\text{CH}_2$	Amide, $\text{RCONHCH}_2\text{OH}$, acid	153 (67)
$(n\text{-C}_7\text{H}_{15}\text{CONH})_2\text{CH}_2$	RCN , $(\text{CH}_3\text{O})_2\text{N}$, acid	503 (good)
$(n\text{-C}_{11}\text{H}_{23}\text{CONH})_2\text{CH}_2$	Amide, formalin, acid RCOCl , hexamine	217 (70), 222 (57) 504 (20)
$[\text{CF}_3\text{CH}_2]_2(\text{CONH})_2\text{CH}_2$	RCN , $(\text{CH}_3\text{O})_2\text{N}$, BF_3 , $\text{CH}_3\text{CO}_2\text{H}$	503 (good)
$(n\text{-C}_{15}\text{H}_{31}\text{CONH})_2\text{CH}_2$	$\text{RCONHCH}_2\text{OH}$, acid, $\text{CH}_3\text{COC}_2\text{H}_5$	217 (poor)
$(n\text{-C}_{17}\text{H}_{33}\text{CONH})_2\text{CH}_2$	RCN , $(\text{CH}_3\text{O})_2\text{N}$, 90% H_2SO_4 RCN , $(\text{CH}_3\text{O})_2\text{N}$, 90% H_2SO_4 $(\text{RCONHCH}_2)_2\text{O}$, acid	503 (good) 503 (100) 217 (100)
	$\text{RCONHCH}_2\text{N}^+\text{C}_6\text{H}_5$  Cl^- , acid	243 (99)
$(n\text{-C}_{11}\text{H}_{23}\text{CONH})_2\text{CH}_2$	$\text{RCONHCH}_2\text{OH}$, acid	235
$(\text{CH}_3)_2\text{CHCONH})_2\text{CH}_2$	RCN , $(\text{CH}_3\text{O})_2\text{N}$, 85% H_2SO_4	4 (86)
	Amide, $(\text{CH}_3\text{O})_2\text{N}$, acid	254 (39), 505 (50)
	$\text{RCONHCH}_2\text{OH}$, acid	254 (67)
$(\text{CH}_2)_2\text{CHCH}_2\text{CONH})_2\text{CH}_2$	RCN , formalin, concd. H_2SO_4	499 (58)
$[\text{CH}_2)_2\text{C}(\text{CH}_3)\text{CONH}]_2\text{CH}_2$	Amide, $\text{RCONHCH}_2\text{OH}$, acid $(\text{RCONHCH}_2)_2\text{O}$, acid, 60°	254 (80)
	$\text{RCONHCH}_2\text{OH}$, acid	424 (81)
	Amide, $(\text{CH}_3)_2\text{N}$, acid	254 (67)
$[(\text{CH}_3)_2\text{C}-\text{CHCONH}]_2\text{CH}_2$	$\text{RCONHCH}_2\text{OH}$, HCl , CCl_4	254 (70), 505 (81) 422 (65)

$(C_4H_5CONH)_2CH_2$	10, 79, 132
$RCONHCH_2OH$, acid	79
$RCONHCH_2OH$, heat	79
$RCONHCH_2OR'$, acid	10 (100), 246, 388
Amide, formalin, acid	495 (good)
Amide, hexamine, base	4 (90), 245, 506, 507
$RCN, (CH_2O)_x, 85-98\% H_2SO_4$	508 (84)
Amide, $RCONHCH_2SO_3Na, NaOC_2H_5, 200^\circ$	509
$RCOCl$, hexamine, base	246
$(C_4H_5CONH)_2Hg, (CH_2S)_3$	465, 497
$RCN, 33\% CH_2O$, concd. HBr	4 (75)
$RCN, (CH_2O)_x, H_2SO_4, CHCl_3$	221
$(RCONHCH_2)_2O$, heat	221
Amide, formalin, acid	221
Amide, formalin, acid	25 (100)
Amide, $RCONHCH_2OH$, acid	132 (100)
$RCONHCH_2OH$, acid	4 (83)
$RCN, (CH_2O)_x, 85\% H_2SO_4$	4 (50), 510 (84)
$RCN, (CH_2O)_x, H_2SO_4, CHCl_3$	510 (95)
Methyl ester, 5% $NaOH, 100^\circ$	
$RCONHCH_2OH, 200^\circ$	430

Lactam, formalin, acid

247, 248

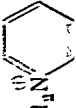


Lactams, Thioamides,
and Imides

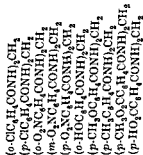


Note: References 382 to 537 are on pp. 268-269.

TABLE XXXII—*Continued*
 SYMMETRICAL, N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
<i>Amides (contd.)</i>		
(<i>n</i> -C ₄ H ₉ CONH) ₂ CH ₂	Amide, RCONHCH ₂ OH, acid RCONHCH ₂ OH, heat	419 (85) 419 (73)
[(C ₂ H ₅) ₂ CHCONH] ₂ CH ₂	Amide, RCONHCH ₂ OH, acid	153 (97)
(<i>n</i> -C ₇ H ₁₅ CONH) ₂ CH ₂	RCN, (CH ₃ O) ₂ C acid	503 (good)
(<i>n</i> -C ₁₁ H ₂₃ CONH) ₂ CH ₂	Amide, formalin, acid RCOCl, hexamine	217 (70), 222 (57) 504 (20)
[CF ₃ (CH ₂) ₁₁ CONH] ₂ CH ₂	RCN, (CH ₃ O) ₂ C HF ₃ , CH ₃ CO ₂ H	503 (good)
(<i>n</i> -C ₁₀ H ₂₁ CONH) ₂ CH ₂	RCONHCH ₂ OH, acid, CH ₃ COC ₂ H ₅	217 (poor)
(<i>n</i> -C ₁₇ H ₃₅ CONH) ₂ CH ₂	RCN, (CH ₃ O) ₂ C 90 % H ₂ SO ₄ RCN, (CH ₃ O) ₂ C 90 % H ₂ SO ₄ (RCONHCH ₂) ₂ O, acid	503 (good) 503 (100) 217 (100)
	 CH ₂ , acid	243 (90)
(<i>n</i> -C ₂₁ H ₄₃ CONH) ₂ CH ₂ (CH ₂ CHCONH) ₂ CH ₂	RCONHCH ₂ OH, acid RCN, (CH ₃ O) ₂ C 85 % H ₂ SO ₄ Amide, (CH ₃ O) ₂ C acid	235 4 (86) 254 (80), 505 (50)
(CH ₂ CHCH ₂ CONH) ₂ CH ₂ [CH ₂ C(CH ₃)CONH] ₂ CH ₂	RCONHCH ₂ OH, acid RCN, formalin, concd. H ₂ SO ₄ Amide, RCONHCH ₂ OH, acid (RCONHCH ₂) ₂ O, acid, 60°	254 (97) 499 (58) 254 (80) 424 (81)
[CH ₂) ₂ C CHCONH] ₂ CH ₂	RCONHCH ₂ OH, acid Amide, (CH ₃ O) ₂ C acid RCONHCH ₂ OH, HCl, CCl ₄	254 (97) 254 (70), 505 (81) 422 (65)

$(C_6H_5CONH)_2CH_2$	RCONHCH ₂ OH, acid	10, 79, 132
	RCONHCH ₂ OR', heat	79
	RCONHCH ₂ OR', acid	79
	Amide, formalin, acid	10 (100), 246, 388
	Amide, hexamine, base	495 (good)
	RCN, (CH ₃ O) ₂ , 85-98% H ₂ SO ₄	4 (90), 245, 506, 507
	Amide, RCONHCH ₂ SO ₃ Na, NaOC ₂ H ₅ , 200°	508 (84)
	RCOCl, hexamine, base	509
	(C ₆ H ₅ CONH) ₂ Hg, (CH ₃ S) ₃	246
	RCN, 33% CH ₂ O, concd. HBr	465, 497
	RCN, (CH ₃ O) ₂ , H ₂ SO ₄ , CHCl ₃	4 (75)
	(RCONHCH ₂) ₂ O, heat	221
	Amide, formalin, acid	221
	Amide, formalin, acid	221
	Amide, RCONHCH ₂ OH, acid	25 (100)
	RCONHCH ₂ OH, acid	132 (100)
	RCN, (CH ₃ O) ₂ , 85% H ₂ SO ₄	4 (83)
	RCN, (CH ₃ O) ₂ , H ₂ SO ₄ , CHCl ₃	4 (50), 510 (84)
	Methyl ester, 5% NaOH, 100°	510 (95)
	RCONHCH ₂ OH, 200°	430
	Lactam, formalin, acid	247, 248



Lactams, Thioamides, and Imides



Note: References 382 to 537 are on pp. 266-269.

TABLE XXXII—Continued
 SYMMETRICAL N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

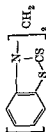
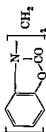
N,N'-Methylene-bis Derivative	Method	References (Yield, %)
<i>Lactams, Thioamides, and Imides</i> (contd.)		
$(\text{CH}_3\text{CSNH})_2\text{CH}_2$ $[o\text{-C}_6\text{H}_4(\text{CO})_2\text{N}]_2\text{CH}_2$	$(\text{CH}_3\text{CONH})_2\text{CH}_2$, P_2S_5 $o\text{-C}_6\text{H}_4(\text{CN})_2$, $(\text{CH}_2\text{O})_x$ H_2SO_4 , CHCl_3 $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NK}$, H^+ $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{N}(\text{CH}_3)_2$, I^- $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NK}$, CH_2I_2 $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NIL}$, hexamino, heat $o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{N}(\text{CH}_3)_2$, 100°	246, 465 4 (20) 81 (48) 256 502 220 (low)
	Imido, formalin, acid	511 (low)
<i>Carbamyl Compounds</i> $(\text{C}_2\text{H}_5\text{O}_2\text{CNH})_2\text{CH}_2$	$\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}_2\text{OH}$, acid $\text{C}_6\text{H}_5\text{O}_2\text{CNH}_2$, formalin, acid CH_3NCO , $\text{CH}_2(\text{OCH}_3)_2$ $\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}_2$, formalin, acid $\text{RO}_2\text{CNHCH}_2\text{CO}_2\text{C}_2\text{H}_5$, $(\text{CH}_2\text{O})_x$, acid, C_6H_6 CH_3NCO , $\text{CH}_2(\text{SC}_2\text{H}_5)_2$ $\text{H}_2\text{NCONHCH}_2\text{OH}$, acid $\text{CO}(\text{NH}_2)_2$, formalin, acid $\text{CH}_3\text{NHCONH}_2$, formalin, acid $\text{C}_2\text{H}_5\text{NHCONH}_2$, formalin, acid	153 250 (85), 251 258 250 (fair), 251 344 (65) 258 146, 147 146, 147, 219 (17) 219 (74), 483 153
$(\text{CH}_3\text{NHCONH})_2\text{CH}_2$ $(\text{C}_2\text{H}_5\text{NHCONH})_2\text{CH}_2$	$(\text{CH}_3\text{O})_2\text{CNCH}_2\text{CH}_2$ $(\text{C}_2\text{H}_5\text{O})_2\text{CNCH}_2\text{CH}_2$ $(\text{C}_6\text{H}_5\text{CH}_2\text{O})_2\text{CNCH}_2\text{CO}_2\text{H}$, CH_2 $[o\text{-C}_6\text{H}_4\text{OC}(-\text{S})\text{NCH}_3]_2\text{CH}_2$ $(\text{H}_2\text{NCONH})_2\text{CH}_2$	

$(\text{CH}_3\text{NHCONCH}_2)_2\text{CH}_2$ $[(\text{CH}_3)_2\text{NCONH}]_2\text{CH}_2$ $(\text{C}_6\text{H}_5\text{NHCONH})_2\text{CH}_2$ $(p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCONH})_2\text{CH}_2$	$\text{CO}(\text{NHCH}_2)_2$, formalin, acid $(\text{CH}_3)_2\text{NCONH}_2$, formalin, acid $(\text{H}_2\text{NCONH})_2\text{CH}_2$, $\text{C}_6\text{H}_5\text{NHCONH}_2$ $p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCONH}_2$, formalin, acid	153 153 475 (60) 55
$\left[\begin{array}{c} \text{CHCO} \\ \diagup \quad \diagdown \\ \text{NCONH} \\ \diagdown \quad \diagup \\ \text{CHCO} \end{array} \right]_2$	NCONH_2 , $(\text{CH}_2\text{O})_x$, concd. H_2SO_4	511α (22)
$(\text{H}_2\text{NCSNH})_2\text{CH}_2$ $(\text{CH}_2\text{NHCSNCH}_2)_2\text{CH}_2$	$\text{CS}(\text{NH}_2)_2$, formalin, acid $\text{CS}(\text{NHCH}_2)_2$, formalin, acid	265 512
$\left[\begin{array}{c} \text{CONH} \\ \diagup \quad \diagdown \\ \text{CO} \\ \diagdown \quad \diagup \\ \text{CH}_2\text{N} \end{array} \right]_2$	Hydantoin, formalin, acid Hydantoin, $(\text{CH}_2\text{O})_x$, concd. HCl Hydantoin, formalin, H_2SO_4 , $\text{CH}_3\text{CO}_2\text{H}$	185 (42) 252 (87) 290 (97)
$\left[\begin{array}{c} \text{CONH} \\ \diagup \quad \diagdown \\ \text{CO} \\ \diagdown \quad \diagup \\ n\text{-C}_3\text{H}_7\text{CHN} \end{array} \right]_2$	<i>n</i> -Propylhydantoin, formalin, ZnCl_2 , concd. HCl	289 (54)
$\left[\begin{array}{c} \text{CONH} \\ \diagup \quad \diagdown \\ \text{CO} \\ \diagdown \quad \diagup \\ i\text{-C}_3\text{H}_7\text{CHN} \end{array} \right]_2$	<i>i</i> -Propylhydantoin, aq. CH_2O , ZnCl_2 , concd. HCl <i>i</i> -Propylhydantoin, formalin, H_2SO_4 , $\text{CH}_3\text{CO}_2\text{H}$	289 (64) 290 (60)

Note: References 382 to 537 are on pp. 268-269.

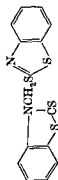
TABLE XXXII—*Continued*
 SYMMETRICAL N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, THIOAMIDES,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
<i>Carbamyl Compounds (contd.)</i>		
$\left[\begin{array}{c} \text{CONH} \\ \diagdown \quad \diagup \\ \text{CO} \\ \diagup \quad \diagdown \\ (\text{CH}_3)_2\text{C}-\text{N}- \end{array} \right]_2 \text{CH}_3$	Dimethylhydantoin, aq. CH_3O , HCl	252 (96)
	Dimethylhydantoin, formalin, ZnCl_2 , concd. HCl	289 (81)
$\left[\begin{array}{c} \text{CONCl} \\ \diagdown \quad \diagup \\ \text{CO} \\ \diagup \quad \diagdown \\ (\text{CH}_3)_2\text{C}-\text{N}- \end{array} \right]_2 \text{CH}_3$	Methylenebisdimethylhydantoin, Cl_2	288 (92)
$\left[\begin{array}{c} \text{OC}-\text{NH} \\ \diagdown \quad \diagup \\ \text{CO} \\ \diagup \quad \diagdown \\ \text{C}_2\text{H}_5\text{C}(\text{CH}_3)\text{N}- \end{array} \right]_2 \text{CH}_3$	Methylethyhydantoin, formalin, ZnCl_2 , concd. HCl	289 (82)
$\left[\begin{array}{c} \text{OC}-\text{NH} \\ \diagdown \quad \diagup \\ \text{CO} \\ \diagup \quad \diagdown \\ i\text{-C}_4\text{H}_9\text{C}(\text{CH}_3)\text{N}- \end{array} \right]_2 \text{CH}_3$	Methyl- <i>i</i> -butylhydantoin, formalin, ZnCl_2 , concd. HCl	289 (67)



3-Chloromethyl-2-benzoxazolone, 2-benzoxazolone

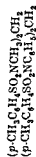
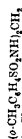
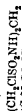
194 (60)



318 (100)

I₂, 200°

Sulfonamides



Amide, formaldehyde, acid

Amide, formalin, K₂CO₃

C₆H₅SO₂NHCH₂OH, C₆H₅, heat

Amide, formalin, K₂CO₃

Amide, formalin, K₂CO₃

ArSO₂NHCH₂OH, C₆H₅, heat

Amide, (CH₃O)₂ HCl

Amide, (CH₃O)₂ HCl

465

85 (70)

156

156

85 (80)

156

158 (47)

156

Note: References 382 to 537 are on pp. 266-269.

TABLE XXXIII

UNSYMMETRICAL N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, IMIDES,
CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFANYL COMPOUNDS

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
Amides		
$\begin{array}{c} \text{HO}_2\text{CCH}_2\text{CONH} \\ \\ \text{CH}_2 \\ \\ \text{CH}_3\text{ClCONH} \end{array}$		
$\begin{array}{c} \text{CH}_3\text{ClCONH} \\ \\ \text{CH}_2 \\ \\ (\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CONH} \end{array}$		465
$\begin{array}{c} \text{CH}_2 \\ \\ (\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CONH} \\ \\ (\text{C}_2\text{H}_5)_2\text{ClCONH} \end{array}$		153
$\begin{array}{c} \text{CH}_2 \\ \\ n\text{-C}_{17}\text{H}_{35}\text{CONH} \\ \\ n\text{-C}_{11}\text{H}_{23}(\text{CH}_2)_3\text{CONH} \end{array}$		217
$\begin{array}{c} \text{CH}_2 \\ \\ n\text{-C}_{17}\text{H}_{35}\text{CONH} \\ \\ \text{NaO}_2\text{SCH}_2\text{CONH} \end{array}$		249
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CHCONH} \\ \\ \text{CH}_2 \\ \\ n\text{-C}_{14}\text{H}_{29}\text{SH} \end{array}$		
$\begin{array}{c} \text{CH}_3\text{CHCONH} \\ \\ \text{CH}_2 \\ \\ n\text{-C}_{17}\text{H}_{35}\text{CONH} \end{array}$		
$\begin{array}{c} \text{CH}_2 \\ \\ \text{CH}_2\text{CHCONH} \\ \\ \text{CH}_2 \\ \\ \text{CH}_2\text{CO}_2\text{Et, 100}^\circ \end{array}$		

$n\text{-C}_{11}\text{H}_{23}\text{CONCH}_2$ CH ₂	$\text{CH}_2(\text{SO}_3\text{Na})\text{CONHCH}_2\text{OH}$, RCONHCH_2 , $\text{CH}_3\text{CO}_2\text{H}$, 100°	249
$\text{NaO}_2\text{SCH}_2\text{CONH}$ CH ₂ =CHCONH	$\text{CH}_3\text{CONHCH}_2\text{OH}$, $\text{CH}_2=\text{CHCONH}_2$, acid, 30-50°	217 (69)
CH_3CONH CH ₂ =CHCONH	$\text{RCONHCH}_2\text{OH}$, $\text{CH}_2=\text{CHCONH}_2$, acid, 50-55°	217 (85)
$n\text{-C}_3\text{H}_{11}\text{CONH}$ CH ₂ =CHCONH	$\text{RCONHCH}_2\text{OH}$, $\text{CH}_2=\text{CHCONH}_2$, acid, 50-55°	217 (81)
$n\text{-C}_7\text{H}_{15}\text{CONH}$ CH ₂ =CHCONH	$\text{RCONHCH}_2\text{OH}$, $\text{CH}_2=\text{CHCONH}_2$, acid, 50-55°	217 (85)
$n\text{-C}_{11}\text{H}_{23}\text{CONH}$ CH ₂ =CHCONH	$\text{RCONHCH}_2\text{OH}$, $\text{CH}_2=\text{CHCONH}_2$, acid, 50-55°	217 (87)

Note: References 382 to 537 are on pp. 266-269.

TABLE XXXIII—Continued
 UNSYMMETRICAL N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, IMIDES,
 CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFAMYL COMPOUNDS

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
<i>Amides (contd.)</i>		
$\begin{array}{c} \text{CH}_2-\text{C}(\text{CH}_3)\text{CONH} \\ \diagup \quad \diagdown \\ \text{CH}_2 \end{array}$	RCONHCH ₂ OH, CH ₃ =C(CH ₃)CONH ₂ , acid, 50–55°	217 (81)
$\begin{array}{c} \text{CH}_2-\text{C}(\text{CH}_3)\text{CONH} \\ \diagup \quad \diagdown \\ \text{n-C}_{17}\text{H}_{33}\text{CONH} \end{array}$	RCONHCH ₂ OH, CH ₃ =C(CH ₃)CONH ₂ , acid, 80°	513 (63)
$\begin{array}{c} \text{CH}_2-\text{CHCONH} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5\text{CONH} \end{array}$	(C ₆ H ₅ CONH) ₂ CH ₂ , (CH ₃ CONH) ₂ CH ₂ , 270°	514 (5)
$\begin{array}{c} \text{CH}_2-\text{CHCONH} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5\text{CONH} \end{array}$	CH ₃ ClCONHCH ₂ OH, C ₆ H ₅ CONH ₂ , acid	465
$\begin{array}{c} \text{CH}_2-\text{CHCONH} \\ \diagup \quad \diagdown \\ \text{C}_2\text{H}_5\text{O}_2\text{C}(\text{CH}_2)_4\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)\text{CONH} \end{array}$	C ₆ H ₅ CONHCH ₂ OH, concd. H ₂ SO ₄ , C ₂ H ₅ O ₂ C(CH ₂) ₄ CH(CO ₂ C ₂ H ₅)CN	84, 119 (91)

$\begin{array}{c} \text{C}_6\text{H}_5\text{CONH} \\ \\ \text{CH}_2 \\ \\ n\text{-C}_{11}\text{H}_{23}\text{CONH} \end{array}$	RCONHCH ₂ OH, C ₆ H ₅ CONH ₂ , HCl, dioxane	249
$\begin{array}{c} \text{C}_6\text{H}_5\text{CONH} \\ \\ \text{CH}_2 \\ \\ \text{CH}_2=\text{CHCONH} \end{array}$	C ₆ H ₅ CONHCH ₂ OH, CH ₂ =CHCN, 99% H ₂ SO ₄ , 30°	255 (60)
$\begin{array}{c} \text{C}_6\text{H}_5\text{CONH} \\ \\ \text{CH}_2 \\ \\ o\text{-HOC}_6\text{H}_4\text{CONH} \end{array}$	ArCONHCH ₂ OH, C ₆ H ₅ CONH ₂ , acid	25 (88)
$\begin{array}{c} \text{NCH}_2\text{NHCO}(\text{CH}_2)=\text{CH}_2 \\ \\ \text{O} \end{array}$	Lactam, RCONHCH ₂ OCH ₃ , NaOC ₂ H ₅ , 130–170°	477
$\begin{array}{c} \text{NCH}_2\text{NHCO}(\text{CH}_2)=\text{CH}_2 \\ \\ \text{O} \end{array}$	Lactam, RCONHCH ₂ OCH ₃ , NaOC ₂ H ₅ , 130–170°	477

Note: References 382 to 537 are on pp. 266–269.

TABLE XXXIII—Continued
 UNSYMMETRICAL N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, IMIDES,
 CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFAMYL COMPOUNDS

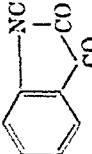
N,N'-Methylene-bis Derivative	Method	References (Yield, %)
<i>Lactams and Imides (contd.)</i>		
		
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{NHCOC}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{CONHCH}_2\text{N}(\text{CH}_3)_2$, isatin, NaOH, $\text{C}_6\text{H}_5\text{CH}_3$, heat	257 (75)
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{N}^-\text{CH}_2$	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OH}$, CH_3CN , concd. H_2SO_4 , 80°	84 (83)
$\text{HO}_2\text{CCCH}_2\text{CONH}$	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OH}$, $\text{NCCCH}_2\text{CO}_2\text{H}$, concd. H_2SO_4 , 45°	84 (91)
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{NHCOC}(\text{CH}_3)=\text{CH}_2$	Imide, $\text{RCONHCH}_2\text{OCH}_3$, NaOC_2H_5 , $130\text{--}170^\circ$	477 (92)
$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{NHCOC}_6\text{H}_5$	Imide, $\text{C}_6\text{H}_5\text{CONHCH}_2\text{SO}_3\text{Na}$, NaOC_2H_5 , 200°	508 (51)
	Imide, $\text{C}_6\text{H}_5\text{CONHCH}_2\text{N}(\text{CH}_3)_2$, NaOH, $\text{C}_6\text{H}_5\text{CH}_3$	257 (68)
	$o\text{-C}_6\text{H}_4(\text{CO})_2\text{NCH}_2\text{OH}$, $\text{C}_6\text{H}_5\text{CN}$, concd. H_2SO_4 , 80°	84 (77)
<i>Carbamyl Compounds</i>		
$\text{C}_2\text{H}_5\text{O}_2\text{CNH}$	$\text{CH}_3\text{ClCONHCH}_2\text{CONHNH}_2$, HNO_2 , $\text{C}_2\text{H}_5\text{OH}$	259 (37), 465
CH_3ClCONH		
$\text{C}_2\text{H}_5\text{O}_2\text{CNH}$		
CH_3BrCONH	$\text{CH}_3\text{BrCONHCH}_2\text{CONHNH}_2$, HNO_2 , $\text{C}_2\text{H}_5\text{OH}$	259 (35)

TABLE XXXIII—Continued

UNSYMMETRICAL N,N'-METHYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS, IMIDES,
CARBAMYL COMPOUNDS, SULFONAMIDES, AND SULFAMYL COMPOUNDS

N,N'-Methylene-bis Derivative	Method	References (Yield, %)
<i>Carbonyl Compounds (contd.)</i>		
		178 (60)
<i>Sulfonamides and Sulfamyl Compounds</i>		
$C_6H_5SO_2NH$	$C_6H_5SO_2NHCH_2OH$, $C_6H_5CONH_2$, xylene	82 (11)
C_6H_5CONH	$C_6H_5CONHCH_2OH$, $C_6H_5SO_2NH_2$, $NaOH$, $C_6H_5CH_3$	257 (80)
$p-CH_3C_6H_4SO_2NCH_3$	$Al_2SO_4NHCH_3$, $C_6H_5CONHCH_2N(CH_3)_2$, $NaOH$, $C_6H_5CH_3$	257 (70)
HO_3SNH	$C_6H_5CONH_2$, H_2NSO_3H , CH_3O , 99 % H_2SO_4 , 70°	515 (20)

Note: References 382 to 537 are on pp. 260-269.

TABLE XXXIV
 SYMMETRICAL N,N'-ALKYLIDENE-BIS AND N,N'-ARYLIDENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Aliphatic Amides</i>			
Formamide and			
Acetaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	4	281
β -Phenylpropionaldehyde	No solvent, heat	0	516
Heptanal	Heat alone, or in $(\text{CH}_3\text{CO})_2\text{O}$, or in pyridine	0	517
Cinnamaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	28	281
Benzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	56	281
o-Chlorobenzaldehyde	No solvent, heat	Poor	287, 518
o-Nitrobenzaldehyde	No solvent, heat	Poor	518
	Pyridine	40	274
m-Nitrobenzaldehyde	No solvent, heat	40	274
p-Nitrobenzaldehyde	No solvent, heat	67	269
3,5-Dichlorosalicylaldehyde	H_2O , acid	68	269
o-Anisaldehyde	No solvent, heat	—	271
m-Anisaldehyde	No solvent, heat	0	296a
p-Anisaldehyde	No solvent, heat	0	296a
	$(\text{CH}_3\text{CO})_2\text{O}$, heat	25	281
Veratraldehyde	No solvent, heat	0	296a
O-Acetylvanillin	$(\text{CH}_3\text{CO})_2\text{O}$, heat	20	281
Piperonal	$(\text{CH}_3\text{CO})_2\text{O}$, heat	21	281
6-Nitropiperonal	No solvent, heat	0	519
p-(CH_3) ₂ NC ₆ H ₄ CHO	No solvent, heat	0	520
m-Tolualdehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	18	281
	Pyridine	48	273

Note: References 382 to 537 are on pp. 266-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued
SYNTHETICAL N,N'-ALKYLIDENE-BIS AND N,N'-ARYLIDENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Aliphatic Amides (contd.)</i>			
Formamide (contd.) and <i>p</i> -Tolualdehyde	Pyridino No solvent, heat (CH_3CO) ₂ O, heat	<50 0 51	276 276 282
1-Naphthaldehyde	(CH_3CO) ₂ O, heat	66	281
Acetamide and Acetaldehyde	$\text{CH}_3\text{CO}_2\text{H}$, heat No solvent, heat $\text{C}_6\text{H}_5\text{OCH}=\text{CH}_2$, heat, acid CH_3CHO , CH_3CN , HCl , H_2O , 300° CCl_3CHO , CH_3CN , concd. H_2SO_4	38, 44 — 82 — —	154, 279 521 233 496 261, 295
Chloral Propionaldehyde	(CH_3CO) ₂ O, heat $\text{CH}_3\text{CO}_2\text{H}$, heat C_6H_6 , heat Pyridino, heat Pyridino	62 35, 7 48 11 9	281 154, 279 283 452 516
β -Phenylpropionaldehyde	No solvent, heat (CH_3CO) ₂ O, heat $\text{CH}_3\text{CO}_2\text{H}$, heat C_6H_6 , heat	26 76 11 49	516 281 279 283
n-Butyraldehyde	(CH_3CO) ₂ O, heat $\text{CH}_3\text{CO}_2\text{H}$, heat $\text{CH}_3\text{CO}_2\text{H}$, heat No solvent, heat	47 26 6 —	281 279 279 517
Isovaleraldehyde	(CH_3CO) ₂ O, heat	54	280
Heptanal			
Cyclohexanecarboxaldehyde	(CH_3CO) ₂ O, heat		


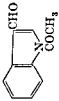
Cinnamaldehyde	(CH ₃ CO) ₂ O, heat	47	281
	C ₆ H ₆ , heat	33	283
	Pyridine	15	275
	No solvent, heat	52	275
Benzaldehyde	(CH ₃ CO) ₂ O, H ₂ SO ₄ , heat	40	85
	(CH ₃ CO) ₂ O, heat	71	281
	CH ₃ CO ₂ H, heat	17	154
	CH ₃ CO ₂ H, heat	48	279
	C ₆ H ₆ , heat	72	283
	No solvent, heat	49	284
	No solvent, heat	—	287, 518, 522, 523
<i>o</i> -Chlorobenzaldehyde	No solvent, heat	Good	518
<i>o</i> -Nitrobenzaldehyde	(CH ₃ CO) ₂ O, heat	67	281
	H ₂ O, acid	—	278
	Pyridine	48	274
<i>m</i> -Nitrobenzaldehyde	No solvent, heat	48	274
	(CH ₃ CO) ₂ O, heat	74	281
	C ₆ H ₆ , heat	44	283
	H ₂ O, acid	—	278
<i>p</i> -Nitrobenzaldehyde	No solvent, heat	60	269
	(CH ₃ CO) ₂ O, heat	61	281
Salicylaldehyde	No solvent, heat	54	269
5-Chlorosalicylaldehyde	C ₆ H ₆ , heat	Poor	283
3,5-Dichlorosalicylaldehyde	No solvent, heat	53	271
<i>o</i> -Anisaldehyde	No solvent, heat	—	271
<i>m</i> -Anisaldehyde	No solvent, heat	40-60	296a
<i>p</i> -Anisaldehyde	C ₆ H ₆ , heat	40-60	296a
	No solvent, heat	84	283
	No solvent, heat	40-60	296a, 524

Note: References 382 to 537 are on pp. 266-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued
 SYMMETRICAL N,N'-ALKYLENE-BIS AND N,N'-ARYLENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Aliphatic Amides (contd.)</i>			
Chloroacetamido (cont.) and			
o-Fluorobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
o-Chlorobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
m-Chlorobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
p-Chlorobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
2,4-Dichlorobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
2,5-Dichlorobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
2,6-Dichlorobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
o-Bromobenzaldehyde	$\text{CH}_3\text{CO}_2\text{H}$, ZnCl_2 , heat	—	465
o-Nitrobenzaldehyde	$\text{CH}_3\text{CO}_2\text{H}$, ZnCl_2 , heat	—	465
m-Nitrobenzaldehyde	No solvent, heat	—	307
p-Nitrobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
	No solvent, heat	—	307
2-Chloro-5-nitrobenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
o-Acetoxybenzaldehyde	$\text{CH}_3\text{CO}_2\text{H}$, heat	—	465
p-Acetoxybenzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
o-Anisaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465
p-Anisaldehyde	$\text{CH}_3\text{CO}_2\text{H}$, heat	—	465
o- $\text{HO}_2\text{CCH}_2\text{OC}_6\text{H}_4\text{CHO}$	$\text{CH}_3\text{CO}_2\text{H}$, heat	—	465
Piperonal	No solvent, heat	—	465
p- $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CHO}$	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	307
p- $\text{CH}_3\text{CONHC}_6\text{H}_4\text{CHO}$	$\text{CH}_3\text{CO}_2\text{H}$, heat	—	465
o- $\text{NCC}_6\text{H}_4\text{CHO}$	$(\text{CH}_3\text{CO})_2\text{O}$, heat	—	465

<i>o</i> -Tolualdehyde	(CH ₃ CO) ₂ O, heat	—	465
<i>m</i> -Tolualdehyde	No solvent, heat	—	307
<i>p</i> -Tolualdehyde	No solvent, heat	—	307
3-Cl-4-CH ₃ C ₆ H ₃ CHO	CH ₃ CO ₂ H, heat	—	465
<i>p</i> -C ₆ H ₄ (CHO) ₂ (<i>bis</i> cpd.)	CH ₃ CO ₂ H, heat	—	465
1-Naphthaldehyde	(CH ₃ CO) ₂ O, heat	—	465
5-Nitro-2-furaldehyde	(CH ₃ CO) ₂ O, heat	—	465
2-Thiophenecarboxaldehyde	(CH ₃ CO) ₂ O, heat	—	307
	(CH ₃ CO) ₂ O, heat	—	465
	(CH ₃ CO) ₂ O, heat	—	465
Pyruvic acid	Heat, in vacuum	—	291, 465
Dichloroacetamide and <i>o</i> -Chlorobenzaldehyde	(CH ₃ CO) ₂ O, heat	—	465
Pyruvic acid	Heat, in vacuum	—	291
Trichloroacetamide and Benzaldehyde	Heat alone or in (CH ₃ CO) ₂ O	0	85
Bromoacetamide and <i>o</i> -Chlorobenzaldehyde	(CH ₃ CO) ₂ O, heat	—	465
Iodoacetamide and <i>o</i> -Chlorobenzaldehyde	<i>o</i> -ClC ₆ H ₄ CH(NHCOCH ₂ Cl) ₂ , KI, CH ₃ OH	—	465

Note: References 382 to 537 are on pp. 266-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued
 SYMMETRICAL N,N'-ALKYLDIENE-BIS AND N,N'-ARYLDIENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Aliphatic Amides (contd.)</i>			
$(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CONH}_2$ and <i>o</i> -Chlorobenzaldehyde	$\text{o-ClC}_6\text{H}_4\text{H}_2\text{CH}(\text{NHCOCH}_2\text{Cl})_2, (\text{C}_2\text{H}_5)_2\text{NH}$	—	465
$\text{N}_2\text{CH}_2\text{CONH}_2$ and <i>o</i> -Chlorobenzaldehyde	$\text{o-ClC}_6\text{H}_4\text{H}_2\text{CH}(\text{NHCOCH}_2\text{Cl})_2, \text{NaN}_3, \text{CH}_3\text{OH}$	—	465
Phenylacetamide and Acetaldehyde	No solvent, heat, acid $n\text{-C}_4\text{H}_9\text{OCH}=\text{CH}_2$, heat, acid $\text{CH}_3\text{CHO}, \text{C}_6\text{H}_5\text{CH}_2\text{CN}$, concd. HCl $\text{CCl}_3\text{CHO}, \text{C}_6\text{H}_5\text{CH}_2\text{CN}$, concd. H_2SO_4 Pyridine or heat alone	— 81 — — 18	526 233 527 201 275
Chloral	No solvent, heat	Good	518
Cinnamaldehyde	No solvent, heat	97	269
<i>o</i> -Chlorobenzaldehyde	No solvent, heat	97	269
<i>m</i> -Nitrobenzaldehyde	No solvent, heat	35	528
<i>p</i> -Nitrobenzaldehyde	No solvent, heat	86	528
5-Chlorosalicylaldehyde	No solvent, heat	40-60	296a
3,5-Dichlorosalicylaldehyde	No solvent, heat	40-60	296a
<i>o</i> -Anisaldehyde	No solvent, heat	40-60	296a
<i>m</i> -Anisaldehyde	No solvent, heat	54	519
<i>p</i> -Anisaldehyde	No solvent, heat	10	520
Piperonal	No solvent, heat	48	273
6-Nitropiperonal	Pyridine		
<i>m</i> -Tolualdehyde			

Propionamide and β-Phenylpropionaldehyde	No solvent, heat	29	516
Heptanal	No solvent, heat	—	517
Cinnamaldehyde	No solvent, heat	51	275
Benzaldehyde	No solvent, heat	45	284, 518
o-Chlorobenzaldehyde	No solvent, heat	Good	518
o-Nitrobenzaldehyde	Pyridine or heat alone	49	274
m-Nitrobenzaldehyde	No solvent, heat	67	269
5-Chlorosalicylaldehyde	No solvent, heat	54	269
3,5-Dichlorosalicylaldehyde	No solvent, heat	—	271
o-Anisaldehyde	No solvent, heat	—	271
m-Anisaldehyde	No solvent, heat	40-60	296a
p-Anisaldehyde	No solvent, heat	40-60	296a
Piperonal	No solvent, heat	40-60	296a
6-Bromopiperonal	No solvent, heat	36	519
6-Nitropiperonal	No solvent, heat	32	525
m-Tolualdehyde	No solvent, heat	15	529
p-Tolualdehyde	Pyridine	36	273
2-Furaldehyde	Pyridine or heat alone	50	270
	No solvent, heat	46	284
CH ₂ ClCH ₂ CONH ₂ and Acetaldehyde	CH ₃ CHO, CH ₂ ClCH ₂ CN, HCl, H ₂ O, 300°	—	465, 496, 500
Benzaldehyde	CH ₃ CO ₂ H, heat	—	465
CH ₂ ClCHClCONH ₂ and Acetaldehyde	CH ₃ CHO, CH ₂ ClCHClCN, HCl, H ₂ O, 250°	—	496, 500
CH ₂ ClCCl ₂ CONH ₂ and Acetaldehyde	CH ₃ CHO, CH ₂ ClCCl ₂ CN, HCl, H ₂ O, 250°	—	500
Benzaldehyde	C ₆ H ₅ CHO, CH ₂ ClCCl ₂ CN, HCl, H ₂ O, 380°	—	465, 500

Note: References 382 to 537 are on pp. 266-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued
 SYMMETRICAL N,N'-ALKYLDIENE-BIS AND N,N'-ARYLDIENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Aliphatic Amides (contd.)</i>			
$\text{CH}_3\text{BrCH}_2\text{CONH}_2$ and Acetaldehyde	$\text{CH}_3\text{CHO}, \text{CH}_2\text{BrCH}_2\text{CN}, \text{HCl}, \text{H}_2\text{O}$, heat	—	500
$\text{CH}_2\text{BrCHBrCONH}_2$ and Acetaldehyde	$\text{CH}_3\text{CHO}, \text{CH}_2\text{BrCHBrCN}, \text{HCl}, \text{H}_2\text{O}$, 380°	—	465, 500
Butyramide and Chloral	$\text{CCl}_3\text{CHO}, \text{RCN}$, 96% H_2SO_4 No solvent, heat	67 22	4 516
β -Phenylpropionaldehyde	RCHO, RCN , 96% H_2SO_4	19	4
Butyraldehyde	Heat alone, or in $(\text{CH}_3\text{CO})_2\text{O}$, or in pyridine	0	517
Heptanal	No solvent, heat	Good	518, 523
Benzaldehyde	No solvent, heat	Good	518
<i>o</i> -Chlorobenzaldehyde	No solvent, heat	65	274
<i>o</i> -Nitrobenzaldehyde	No solvent, heat	84	269
<i>m</i> -Nitrobenzaldehyde	No solvent, heat	72	269
<i>p</i> -Nitrobenzaldehyde	No solvent, heat	—	271
5-Chlorosalicylaldehyde	No solvent, heat	—	271
3,5-Dichlorosalicylaldehyde	No solvent, heat	55	519
Piperonal	No solvent, heat	57	520
6-Nitropiperonal	No solvent, heat	39	273
<i>m</i> -Tolualdehyde	Pyridine	—	
$\text{HO}_2\text{C}(\text{CH}_2)_4\text{CONH}_2$ and Acetaldehyde	$\text{CH}_3\text{CHO}, \text{HO}_2\text{C}(\text{CH}_2)_4\text{CN}$, concd. HCl $\text{CH}_3\text{CHO}, \text{HO}_2\text{C}(\text{CH}_2)_4\text{CN}, \text{HCl}, \text{H}_2\text{O}$, 250°	— —	497 496, 500

Heptanamide and

β-Phenylpropionaldehyde

Heptanal

Cinnamaldehyde

Benzaldehyde

o-Chlorobenzaldehyde

o-Nitrobenzaldehyde

m-Nitrobenzaldehyde

p-Nitrobenzaldehyde

3,5-Dichlorosalicylaldehyde

Piperonal

6-Bromopiperonal

6-Nitropiperonal

m-Tolualdehyde

Cyclohexanecarboxamide and

Acetaldehyde

Benzaldehyde

Acrylamide and

Octanal

Benzaldehyde

Cinnamamide and

Heptanal

Benzaldehyde

5-Chlorosalicylaldehyde

3,5-Dichlorosalicylaldehyde

Piperonal

6-Nitropiperonal

No solvent, heat
Heat alone, or in $(\text{CH}_3\text{CO})_2\text{O}$, or in pyridine
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
No solvent, heat
Pyridine or heat alone

40

0

41

Good

Good

100

97

97

—

77

36

55

<40

516

517

530

518

518

274

260

269

271

519

525

520

273

$(\text{CH}_3\text{CO})_2\text{O}$, heat

$(\text{CH}_3\text{CO})_2\text{O}$, heat

268

268

Concd. HCl, heat

Concd. HCl, heat

505

505

No solvent, heat

No solvent, heat

No solvent, heat

No solvent, heat

No solvent, heat

No solvent, heat

No solvent, heat

517

284, 518

528

528

519

520

Note: References 382 to 537 are on pp. 266-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued
 SYMMETRICAL N,N'-ALKYLDIENE-BIS AND N,N'-ARYLDIENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2RCONH_2 + R'CHO \rightarrow (RCONH)_2CHR'$

Derivative of	Method*	Yield, %	References
<i>Aliphatic Amides (contd.)</i>			
α -Methylcinnamamide and Benzaldehyde	No solvent, heat	48	284
$(CONH_2)_2$ and Benzaldehyde	$C_2H_5O_2CCONH_2$, C_6H_5CHO , 150° $\left(\begin{array}{c} CONH \\ \\ \text{Product: } \begin{array}{c} \diagup \quad \diagdown \\ \quad \\ CHC_6H_5 \\ \quad \\ CONH \end{array} \\ \diagdown \quad \diagup \end{array} \right)$	—	285
$(C_2H_5)_2C(CONH_2)_2$ and Cinnamaldehyde	No solvent, acid, 150° No solvent, acid, 150° $\left(\begin{array}{c} CONH \\ \\ \text{Products: } (C_2H_5)_2C \begin{array}{c} \diagup \quad \diagdown \\ \quad \\ CHR \\ \quad \\ CONH \end{array} \\ \diagdown \quad \diagup \end{array} \right)$	— —	286 286
$(CH_2CONHC_6H_5)_2$ and Heptanal	No solvent, 110° (product not characterized)	—	270

Aromatic Amides

Benzamide and

Acetaldehyde

	(CH ₃ CO) ₂ O, heat	48	281
	H ₂ O, acid	—	531
	<i>n</i> -C ₄ H ₉ OCH=CH ₂ , C ₆ H ₅ CONH ₂ , heat	63, 80	232, 233
	CH ₃ CHO, C ₆ H ₅ CN, concd. H ₂ SO ₄	—	245, 527
	CH ₃ CHO, C ₆ H ₅ CN, HCl, H ₂ O, 300°	—	496
	CH ₃ CHO, NH ₄ OH, C ₆ H ₅ COCl	—	532
Chloral	[C ₆ H ₅ CONHCH(CCl ₃) ₂] ₂ O, 140°/40 mm.	—	95
	CCl ₃ CHO, C ₆ H ₅ CN, concd. H ₂ SO ₄	37	245, 261, 296
Bromal	CCl ₃ CHO, C ₆ H ₅ CONH ₂ , concd. H ₂ SO ₄	67	296
β-Phenylpropionaldehyde	CBBr ₃ CHO, C ₆ H ₅ CN, concd. H ₂ SO ₄	—	245
Valeraldehyde	No solvent, heat	40	275, 516
Heptanal	RCHO, C ₆ H ₅ CN, concd. H ₂ SO ₄	—	245
Cyclohexanecarboxaldehyde	<i>n</i> -C ₄ H ₉ CHO, C ₆ H ₅ CN, concd. H ₂ SO ₄	—	245
Cinnamaldehyde	No solvent, heat	—	285, 517
Benzaldehyde	(CH ₃ CO) ₂ O, heat	69	280
	No solvent, heat	55	275
	(CH ₃ CO) ₂ O, heat	43	281
	(CH ₃ CO) ₂ O, heat	78	85
	No solvent, heat	27	284
	No solvent, heat	—	518, 522, 523, 533
<i>o</i> -Chlorobenzaldehyde	No solvent, heat	Good	518
<i>o</i> -Nitrobenzaldehyde	H ₂ O, acid	—	278
	No solvent, heat	64	274
	H ₂ O, acid	—	278
<i>m</i> -Nitrobenzaldehyde	No solvent, heat	80	269

Note: References 382 to 537 are on pp. 266-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued
 SYMMETRICAL N,N'-ALKYLIDENE-BIS AND N,N'-ARYLDENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Aromatic Amides (contd.)</i>			
Benzamide (contd.) and			
<i>p</i> -Nitrobenzaldehyde	No solvent, heat	80	269
5-Chlorosalicylaldehyde	Pyridine	—	271
3,5-Dichlorosalicylaldehyde	No solvent, heat	—	271
<i>o</i> -Anisaldehyde	No solvent, heat	40–60	296a
<i>m</i> -Anisaldehyde	No solvent, heat	40–60	296a
<i>p</i> -Anisaldehyde	No solvent, heat	40–60	296a, 524
Piperonal	No solvent, heat	64	519
6-Bromopiperonal	No solvent, heat	4	525
6-Nitropiperonal	No solvent, heat	25	520
<i>m</i> -Tolualdehyde	No solvent, heat	37	273
<i>p</i> -Tolualdehyde	Pyridine	50	276
1-Naphthaldehyde	Pyridine or heat alone	43	282
2-Naphthaldehyde	(CH ₃ CO) ₂ O, heat	59	282
9-Anthraldehyde	(CH ₃ CO) ₂ O, heat	38	282
1-Pyrene-carboxaldehyde	(CH ₃ CO) ₂ O, heat	75	282
2-Furaldehyde	No solvent, heat	40	284
2-Thiophene-carboxaldehyde	(CH ₃ CO) ₂ O, heat	68	280, 282
2-Pyrole-carboxaldehyde	(CH ₃ CO) ₂ O, heat	0	280
Picolinaldehyde	No solvent, heat	99	280
Nicotinaldehyde	No solvent, heat	73	280
Isonicotinaldehyde	No solvent, heat	27	280
3-Indole-carboxaldehyde	(CH ₃ CO) ₂ O, heat	60	280
Benzamide and Heptand	No solvent, 110°	—	270

<i>o</i> -Chlorobenzamide and Acetaldehyde	CH ₃ CHO, ArCN, concd. HBr CH ₃ CHO, ArCN, HCl, H ₂ O, 280°	— —	497 500
<i>p</i> -Chlorobenzamide and Chloral	CCl ₃ CHO, ArCN, 95% H ₂ SO ₄	—	206
<i>o</i> -Nitrobenzamide and Benzaldehyde	(CH ₃ CO) ₂ O, HCl, heat	40	85
<i>α</i> -Nitrobenzamide and Heptanal	No solvent, heat	—	285
<i>o</i> -Anisamide and Benzaldehyde	H ₂ O, acid	—	305
<i>o</i> -Toluidine and <i>o</i> -Nitrobenzaldehyde	No solvent, heat	47	274
2-CH ₃ -5-O ₂ -NC ₆ H ₃ CONH ₂ and Benzaldehyde	No solvent, heat	—	534
<i>m</i> -Nitrobenzaldehyde	No solvent, heat	—	534
<i>p</i> -Nitrobenzaldehyde	No solvent, heat	—	534
Piperonal	No solvent, heat	—	534
<i>p</i> -Toluidine and Chloral	CCl ₃ CHO, ArCN, 95% H ₂ SO ₄	40	290
1-Naphthamide and Acetaldehyde	(CH ₃ CO) ₂ O, heat	58	268
Benzaldehyde	No solvent, heat	93	268
Nicotinamide and Acetaldehyde	No solvent, heat	9	268
Benzaldehyde	No solvent, heat	66	268

Note: References 382 to 537 are on pp. 266-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

TABLE XXXIV—Continued
 SYMMETRICAL N,N'-ALKYLDIENE-BIS AND N,N'-ARYLDIENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Lactams and Imides</i>			
2-Pyrrolidinone and Acetaldehyde	H_2O , acid	Good	247
Phthalimide and Benzaldehyde	$(\text{CH}_3\text{CO})_2\text{O}$, heat	0	85
<i>Carbonyl Compounds</i>			
Ethyl carbamate and Acetaldehyde	H_2O , acid	78	173, 250, 531
Chloroacetaldehyde	H_2O , acid	—	173
	$\text{C}_2\text{H}_5\text{OH}$, HCN , Cl_2	—	266, 267
	H_2O , acid	—	173
	$\text{C}_2\text{H}_5\text{OH}$, HCN , Cl_2	—	266, 267
Dichloroacetaldehyde	$\text{NH}_2\text{CO}_2\text{C}_2\text{H}_5$, $(\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}(\text{CCl}_3)_2)_2\text{O}$	38	94
	$\text{NH}_2\text{CO}_2\text{C}_2\text{H}_5$, Cl_2	20	94
	$\text{NH}_2\text{CO}_2\text{C}_2\text{H}_5$, CCl_3CHO , acid	—	94
Chloral	$[\text{C}_2\text{H}_5\text{O}_2\text{CNHCH}(\text{CCl}_3)_2]_2\text{O}$, PCl_5	—	95
Bromoacetaldehyde	$\text{NH}_2\text{CO}_2\text{C}_2\text{H}_5$, Br_2	—	230
Dibromoacetaldehyde	$\text{NH}_2\text{CO}_2\text{C}_2\text{H}_5$, Br_2	—	230
Bromal	H_2O , acid	—	173
	$\text{C}_2\text{H}_5\text{OH}$, HCN , Br_2	—	267
	$\text{NH}_2\text{CO}_2\text{C}_2\text{H}_5$, Br_2	—	535
	$\text{NH}_2\text{CO}_2\text{C}_2\text{H}_5$, CBr_3CHO , acid	27	535

Valeraldehyde	H ₂ O, acid	173
Cinnamaldehyde	H ₂ O, acid	277
Glyoxylic acid	Heat alone	230
Benzaldehyde	H ₂ O, acid	173
<i>o</i> -Nitrobenzaldehyde	NaOC ₂ H ₅	230
<i>m</i> -Nitrobenzaldehyde	H ₂ O, acid	278
<i>p</i> -Anisaldehyde	H ₂ O, acid	278
Piperonal	H ₂ O, acid	277
2-Furaldehyde	H ₂ O, acid	529
<i>n</i> -Propyl carbamate and Acetaldehyde	H ₂ O, acid	277
Benzaldehyde	H ₂ O, acid	277
NH ₂ CS(OC ₂ H ₅) and Valeraldehyde	H ₂ O, acid	277
Urea and†		
Chloral		
CH ₃ CHClCCl ₂ CHO	H ₂ NCONHCHOHCCl ₃ , urea, (CH ₃ CO) ₂ O	
Valeraldehyde	Heat alone	473
Heptanal	Heat alone	536
Acrolein	H ₂ O alone	536
Cinnamamide	C ₂ H ₅ OH alone	272
Benzaldehyde	H ₂ O alone	272
<i>α</i> -Nitrobenzaldehyde	C ₂ H ₅ OH alone	272
Salicylaldehyde	C ₂ H ₅ OH alone	123, 272
	C ₂ H ₅ OH alone	272
		272
		272

Note References 382 to 537 are on pp. 268-269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

† The products are of the type (H₂NCONH)₂CHR.

TABLE XXXIV—Continued
 SYMMETRICAL N,N'-ALKYLDIENE-BIS AND N,N'-ARYLDIENE-BIS DERIVATIVES OF AMIDES, LACTAMS,
 IMIDES, CARBAMYL COMPOUNDS, AND SULFONAMIDES
 $2\text{RCONH}_2 + \text{R}'\text{CHO} \rightarrow (\text{RCONH})_2\text{CHR}'$

Derivative of	Method*	Yield, %	References
<i>Carbamyl Compounds (contd.)</i>			
Urea (contd.) and†			
5-Chlorosalicylaldehyde	$\text{C}_2\text{H}_5\text{OH}$ alone	—	271
3,5-Dichlorosalicylaldehyde	$\text{C}_2\text{H}_5\text{OH}$ alone	—	271
<i>p</i> -Anisaldehyde	$\text{C}_2\text{H}_5\text{OH}$ alone	—	272
<i>o</i> -Ethoxybenzaldehyde	$\text{C}_2\text{H}_5\text{OH}$ alone	—	272
Cumaldehyde	$\text{C}_2\text{H}_5\text{OH}$ alone	—	123
Hydantoin and	Hydantoin, $\text{CH}_3(\text{OC}_2\text{H}_5)_2$, $\text{CH}_3\text{CO}_2\text{H}$, H_2SO_4 , heat	96	290
Acetaldehyde	Hydantoin, $\text{CH}_3\text{ClCH}(\text{OC}_2\text{H}_5)_2$, $\text{CH}_3\text{CO}_2\text{H}$, H_2SO_4 , heat	70	290
Chloroacetaldehyde			
<i>Sulfonamides</i>			
<i>p</i> -Toluenesulfonamide and			
Acetaldehyde	ArSO_2NH_2 , $\text{C}_6\text{H}_5\text{OCH}=\text{CH}_2$, acid	11	232

Note: References 382 to 537 are on pp. 266–269.

* Except when otherwise indicated, the amide and aldehyde are unnamed reactants in this column.

† The products are of the type $(\text{H}_2\text{NCONH})_2\text{CHR}$.

TABLE XXXV


UNSYMMETRICAL N,N'-ARYLIDENEBISAMIDES²³⁴

$\text{RCONH}_2 + \text{R}'\text{CONH}_2 + \text{ArCHO} \xrightarrow[\text{No solvent}]{\text{Heat}} \text{RCONHCH(Ar)NHCOR}'$			
R	R'	Ar	Yield, %
CH ₃	C ₂ H ₅	C ₆ H ₅	30
CH ₃	C ₆ H ₅ CH=CH	C ₆ H ₅	39
CH ₃	C ₆ H ₅ CH=C(CH ₃)	C ₆ H ₅	38
CH ₃	C ₆ H ₅	C ₆ H ₅	42
CH ₃	C ₂ H ₅	2-Furyl	25
CH ₃	C ₆ H ₅ CH=CH	2-Furyl	26
C ₂ H ₅	C ₆ H ₅ CH=CH	C ₆ H ₅	33
C ₂ H ₅	C ₆ H ₅ CH=C(CH ₃)	C ₆ H ₅	30
C ₂ H ₅	C ₆ H ₅	C ₆ H ₅	38
C ₆ H ₅ CH=CH	C ₆ H ₅ CH=C(CH ₃)	C ₆ H ₅	25
C ₆ H ₅ CH=CH	C ₆ H ₅	C ₆ H ₅	29
C ₆ H ₅ CH=C(CH ₃)	C ₆ H ₅	C ₆ H ₅	26

Note: References 382 to 537 are on pp. 266-269.

TABLE XXXVI

AMIDOMETHANESULFONIC ACIDS AND SALTS

Sulfonic Acid Derivative	References (Yield, %)
CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ CONHCH ₂ SO ₃ Na	537
C ₆ H ₅ CONHCH ₂ SO ₃ Na	132
p-CH ₃ OC ₆ H ₄ CONHCH ₂ SO ₃ Na	132 (60)
o-C ₆ H ₄ (CO) ₂ NCH ₂ SO ₃ H	309 (13)
C ₆ H ₅ SO ₂ NHCH ₂ SO ₃ Na	132
SO ₂ NHCH ₂ SO ₃ Na	
 SO ₂ NHCH ₂ SO ₃ Na	132

Note: References 382 to 537 are on pp. 266-269.

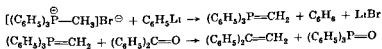
- ⁴²⁷ Suter, Stocker, and Zutter, U.S. pat. 2,660,592 [C.A., 48, 8271 (1954)].
⁴²⁸ Suter, Habicht, and Kundig, Can. pat. 511,544 (1955).
⁴²⁹ Offe and Siefken, Ger. pat. 919,351 [C.A., 52, 14706 (1958)].
⁴³⁰ Martin, Habicht, and Zutter, U.S. pat. 2,741,620 [C.A., 51, 7445 (1957)].
⁴³¹ Cherbuliez and Chambers, *Helv. Chim. Acta.*, 8, 395 (1925).
⁴³² Tawney, U.S. pat. 2,743,260 [C.A., 50, 11716 (1956)].
⁴³³ Drábek, *Chem. Zvesti*, 12, 29 (1958) [C.A., 52, 13705 (1958)].
⁴³⁴ Sachs, *Ber.*, 31, 3230 (1898).
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⁴³⁶ Vasa and Kshatriya, *J. Indian Chem. Soc.*, 36, 527 (1959) [C.A., 54, 9837 (1960)].
⁴³⁷ Maselli, *Gazz. Chim. Ital.*, 30 (II), 31 (1900) (*Chem. Zentr.*, 1900, II, 629).
⁴³⁸ Schroy, U.S. pat. 2,361,322 [C.A., 39, 2228 (1945)].
⁴³⁹ Einhorn and Göttinger, *Ann.*, 361, 148 (1908).
⁴⁴⁰ Dixon, *J. Chem. Soc.*, 113, 238 (1918).
⁴⁴¹ Dunn, *J. Chem. Soc.*, 1957, 1446.
⁴⁴² Einhorn and Hamburger, *Ber.*, 41, 24 (1908).
⁴⁴³ Scheibler, Trostler, and Scholz, *Angew. Chem.*, 41, 1305 (1928).
⁴⁴⁴ Walter and Gewing, *Kolloid-Beih.*, 34, 163 (1931); Walter, Ger. pat. 519,322 (*Chem. Zentr.*, 1928, II, 1383) [C.A., 26, 5183 (1932)].
⁴⁴⁵ Pollopos Ltd., Ger. pat. 504,863 (*Chem. Zentr.*, 1930, II, 2050).
⁴⁴⁶ Alexander, Carter, and Earland, *Melliand Textilber.*, 32, 238 (1951).
⁴⁴⁷ Imperial Chemical Industries Ltd., British pat. 577,735 [C.A., 41, 2254 (1947)].
⁴⁴⁸ Farlow, U.S. pat. 2,422,400 [C.A., 41, 6279 (1947)].
⁴⁴⁹ Wayland, U.S. pat. 2,825,732 [C.A., 52, 14686 (1958)].
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^{453a} Reid, Frick, Reinhardt, and Arceneaux, *Am. Dyestuff Repts.*, 43, 81 (1959) [C.A., 53, 8637 (1959)].
⁴⁵³ Walker, Brit. pat. 564,424 [C.A., 40, 3300 (1946)].
⁴⁵⁴ Jaffe, *Ber.*, 35, 2896 (1902).
⁴⁵⁵ Arnold and Vogelsang, Ger. pat. 1,016,267 [C.A., 53, 22019 (1959)].
⁴⁵⁶ July, Knott, and Pollak, U.S. pat. 2,732,316 [C.A., 50, 7640 (1956)].
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⁴⁶² Wallach, *Ber.*, 5, 254 (1872).
⁴⁶³ Schiff and Tassinari, *Ber.*, 10, 1783 (1877).
⁴⁶⁴ Pinner, *Ann.*, 179, 40 (1875).
⁴⁶⁵ Schraufstatter and Gönner, *Z. Naturforsch.*, 17b, 505 (1962) [C.A., 57, 13668 (1962)].
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⁴⁷⁴ Kalle and Co., in Biebrich, Ger. pat. 128,462 (*Chem. Zentr.*, 1902, I, 547).
⁴⁷⁵ Zigeuner, Pitter, Berger, and Rauch, *Monatsh. Chem.*, 83, 165 (1953).
⁴⁷⁶ Robson and Reinhart, *J. Am. Chem. Soc.*, 77, 2453 (1955).

- ⁵²³ Pandya and Sethi, *J. Indian Chem. Soc.*, **25**, 145 (1948) [*C.A.*, **44**, 3465 (1950)].
⁵²⁴ Bernthsen, *Ann.*, **184**, 318 (1877).
⁵²⁵ Henle and Schupp, *Ber.*, **38**, 1369 (1905).
⁵²⁶ Nigam and Pandya, *Proc. Indian Acad. Sci.*, **29A**, 364 (1949) [*C.A.*, **44**, 1454 (1950)].
⁵²⁷ Bianchi, *Gazz. Chim. Ital.*, **43** (I), 237 (1913) (*Chem. Zentr.*, **1913**, I, 1962).
⁵²⁸ Pandya and Bhandari, *J. Indian Chem. Soc.*, **24**, 209 (1947) [*C.A.*, **43**, 2600 (1949)].
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⁵³⁰ Limpriht, *Ann.*, **99**, 119 (1856).
⁵³¹ Hoffmann and Meyer, *Ber.*, **25**, 209 (1892).
⁵³² Macovski and Bachmeyer, *Ber.*, **77**, 487 (1944).
⁵³³ Diels and Ochs, *Ber.*, **40**, 4571 (1907).
⁵³⁴ Pinner and Lifschütz, *Ber.*, **20**, 2345 (1887).
⁵³⁵ Yamashita and Yoshizaki, U.S. pat. 2,313,695 [*C.A.*, **37**, 5168 (1943)].

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1-Chloro-2,6-dimethyl-1,5-heptadiene	398
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INTRODUCTION

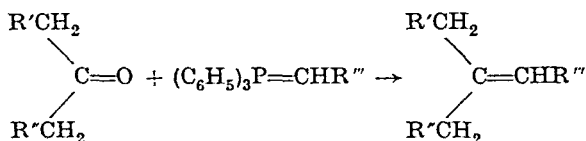
In 1953 Wittig and Geissler¹ found that reaction of benzophenone with methylenetriphenylphosphorane gave 1,1-diphenylethylene and triphenylphosphine oxide in almost quantitative yield; the phosphorane had been prepared from triphenylmethylphosphonium bromide and phenyllithium. This discovery led in the following years to the development of



¹ Wittig and Geissler, *Ann*, 580, 44 (1953)

a new method for the synthesis of olefins²⁻⁶ which, under the name Wittig reaction, soon attained importance in preparative organic chemistry.

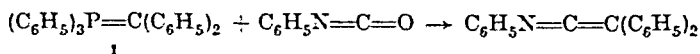
One advantage of this new method is that the carbonyl group is replaced specifically by a carbon-carbon double bond without the formation of isomeric olefins. In contrast, the older method of converting carbonyl



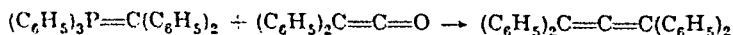
compounds to olefins using the Grignard reaction followed by dehydration of the resulting carbinol usually gives a mixture of isomeric olefins.

Another advantage of the Wittig reaction is that it is carried out in alkaline medium and usually under very mild conditions. Consequently it is the only method available for the preparation of sensitive olefins such as carotenoids, methylene steroids, and other natural products.

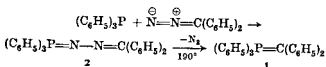
As early as 1919 Staudinger and Meyer^{7,8} showed that the reaction of diphenylmethylenetriphenylphosphorane (1) with phenyl isocyanate gave N-phenyldiphenylketeneimine; but this discovery did not lead to the



discovery of a new synthesis of olefins. One reason is the unusual stability of the phosphorane 1, which could not be made to react with normal carbonyl compounds. It has been found that, even with diphenylketene, reaction will occur only under forcing conditions (at 140° in benzene under pressure).⁹⁻¹¹



obtained from triphenylphosphine and diphenyldiazomethane. This



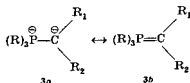
roundabout method could not be extended to the preparation of other phosphoranes since, in the pyrolysis of phosphazines, ketazines are usually formed instead.⁷ It was not until the development of modern techniques in organometallic chemistry that reactive methylene phosphoranes became easily accessible and led to routes to olefins in good yields from a variety of aldehydes and ketones

This chapter includes the more important literature to the end of 1962 and a few selected articles published in 1963. Other reviews have been published elsewhere.^{12-17a}

ALKYLIDENE TRIPHENYLPHOSPHORANES

Structure and Properties of Ylides

The existence of pentaphenylphosphorane¹⁸ shows that, unlike nitrogen, phosphorus is capable of being pentavalent, since it can expand its valency shell to 10 electrons by inclusion of *d* orbitals. Alkylidene phosphoranes can therefore be considered as resonance hybrids of two limiting structures, the ylide form **3a** and the ylene form **3b**. An in-



dication that alkylidene phosphoranes possess some ylene character was obtained from a kinetic study which showed that tetramethylphosphonium iodide is converted to the ylide much faster than is tetramethylammonium iodide, despite the fact that the protons in the phosphonium salt are under the influence of weaker repulsive Coulomb forces than those

¹² Levisalles, *Bull. Soc. Chim. France*, 1958, 1021.

¹³ Schöllkopf, *Angew. Chem.*, 71, 260 (1959).

¹⁴ Pelc, *Chem. Listy*, 53, 177 (1959) [*C.A.*, 53, 7965a (1959)].

¹⁵ Kostka, *Wiadomości Chem.*, 12, 521 (1958).

¹⁶ Trippett, *Advan. Org. Chem.*, 1, 83 (1960).

¹⁷ Yanovskaya, *Usp. Khim.*, 30, 813 (1961) [*C.A.*, 56, 1323a (1962)].

^{17a} Trippett, *Quart. Rev.*, 17, 406 (1963).

¹⁸ Wittig and Rieber, *Ann.*, 562, 187 (1949).

in the ammonium salt (bond distances: P—C, 1.87 Å; N—C, 1.47 Å).¹⁹ This greater tendency for the formation of phosphorus ylides reflects stabilization of the transition state by *p-d* orbital overlap.

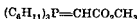
The reactivity of alkylidene phosphoranes is determined by the distribution of the negative charge in the molecule, which in turn depends on the nature of the substituents R_1 and R_2 in the alkylidene portion as well as of the groups R on phosphorus. Thus the nucleophilic character of the phosphorane is decreased and the stability of the phosphorane increased if the lone electron pair on the α -carbon atom of form **3a** is delocalized into groups R_1 and R_2 . Generally speaking, electron-withdrawing substituents R_1 and R_2 will stabilize the negative charge and consequently reduce the reactivity of the ylide. Methylenetriphenylphosphorane (**3a**, **3b**, $R_1 = R_2 = H$), where there is no such interaction, is an extremely reactive and unstable phosphorane of high nucleophilicity.

The groups R on phosphorus also influence the reactivity of the alkylidene phosphoranes since they may be capable of increasing or decreasing the *d*-orbital resonance with a consequent change in the relative importance of form **3b** in the resonance hybrid. Decreased *d*-orbital resonance would result in greater importance of the ylide form **3a** and therefore increased reactivity of the phosphorane. Investigations of the ultraviolet spectra of polyphenyl derivatives of phosphorus led to the conclusion that the formation of double bonds with inclusion of *d* orbitals is possible only if the central atom is positively charged in the single-bonded structure.²⁰⁻²² Applied to the alkylidene phosphoranes, this would mean that the ylene form **3b** would be the more important the larger the formal charge on phosphorus. Electron-withdrawing groups R on phosphorus will, other things being equal, increase the *d*-orbital resonance and therefore favor the ylene form **3b**, whereas electron-releasing groups will increase the importance of the ylide form **3a**. These hypotheses are supported by investigations of transition metal complexes in which trivalent phosphorus occurs as a ligand and forms π as well as σ bonds with the metal. It has been shown that the capability for the formation of π bonds decreases in the series: $PF_3 > PCl_3 > P(OCH_3)_3 > P(C_3H_7-\pi)_3$, i.e., in the same sequence as the positive inductive effect ($+\text{I}$ effect) of substituents on phosphorus.²³

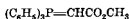
Subsequently, studies were made of the ultraviolet and visible spectra of a series of planar complexes of the structure *trans*-[L, piperidine $PtCl_2$], where the ligand L was an aliphatic amine, phosphine, etc. Again

the extent of the phosphorus *d*-orbital participation in the interaction with the metal increases with increasing +I effect of the groups on phosphorus: $L = P(C_3H_7-n)_3 < L = P(OCH_3)_3$.²⁴ Finally, studies of the carbonyl stretching frequency in the infrared spectra of nickel dicarbonyl-diphosphines $[Ni(CO)_2(PR_3)_2]$ ²⁵ and of complexes of the structure $(PR_3)_3Cr(CO)_3$ ²⁶ showed that the *d*-orbital participation in the metal phosphorus bond decreases in the series $PCl_3 > P(OC_6H_5)_3 > P(OC_2H_5)_3 > P(C_6H_5)_3 > P(C_4H_9-n)_3$, i.e., again following the +I effect. Similar results using ³¹P nuclear magnetic resonance spectroscopy were obtained.²⁷

It would therefore be expected that alkylidene trialkylphosphoranes, in which the formal positive charge on phosphorus is reduced by the inductive effect of the alkyl groups, would under otherwise equal conditions be more reactive than alkylidene triphenylphosphoranes in which the +I effect of the phenyl groups has the opposite effect. This is the case. Carbomethoxymethylenetricyclohexylphosphorane (4), for instance, is a stronger base than carbomethoxymethylenetriphenylphosphorane (5), and, unlike the latter, is sensitive to water.²⁸ The same explanation



4



5

rationalizes the increased stability of fluorenylidenetriphenylphosphorane toward hydrolysis as compared to that of fluorenylidene trialkylphosphoranes.²⁹ In general, the conjugate acid of a phosphorane should be the stronger the more important the ylene form 3b (and consequently the more important the *d*-orbital resonance); i.e., a more acidic phosphonium salt will be related to a less reactive phosphorane, and vice versa. It is possible to estimate the reactivity of an ylde from the pK_a value of its conjugate acid.²⁹

The discussion of the mechanism of the Wittig reaction will show, however, that alkylidene trialkylphosphoranes are superior to alkylidene triphenylphosphoranes only in certain special cases.

The Wittig reagents may be divided into two groups according to their reactivity. The first and larger group includes the alkylidene phosphoranes of low stability and high reactivity, whereas the second group comprises the highly stable unreactive resonance-stabilized alkylidene phosphoranes.

²⁴ Chatt, Gamlen, and Orgel, *J. Chem. Soc.*, 1959, 1047.

²⁵ Meriwether and Fieno, *J. Am. Chem. Soc.*, **81**, 4200 (1959).

²⁶ Abel, Bennett, and Wilkinson, *J. Chem. Soc.*, 1959, 2323.

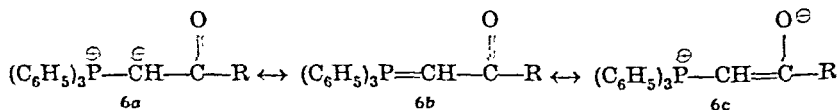
²⁷ Meriwether and Leto, *J. Am. Chem. Soc.*, **83**, 3192 (1961).

²⁸ Bestmann and Kratzer, *Chem. Ber.*, **95**, 1894 (1962).

²⁹ Johnson and LaCount, *Tetrahedron*, **9**, 130 (1960).

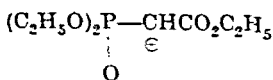
Phosphoranes containing substituents in the alkylidene group that have little effect on the carbanion character of the molecule are found in the first group. These Wittig reagents are markedly nucleophilic and react readily at low temperatures with carbonyl and other polar groups.

The second group consists of phosphoranes with electron-withdrawing substituents in the alkylidene portion which decrease the nucleophilicity to a certain extent and, in some cases, completely prevent the attack on a carbonyl group. Unlike the phosphoranes of the first group, they are essentially stable toward hydrolysis. For instance, the acylmethylene triphenylphosphoranes^{30,31} are colorless crystalline compounds that are hydrolyzed only at elevated temperatures. This stability is probably due to resonance between the limiting structures **6a** to **6c** in which the carbonyl group is included. This is reflected in the shift of the carbonyl band in the infrared spectrum to 6.5–6.7 μ .³² In spite of this resonance stabi-



lization the acylmethylene triphenylphosphoranes undergo the Wittig reaction with reactive carbonyl compounds such as benzaldehyde, but not with cyclohexanone under the same conditions.³¹ Similarly formylmethylenetriphenylphosphorane (**6**, R = H), a stable compound of melting point 187°, reacts readily with aldehydes in boiling benzene but not with ketones.³³

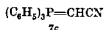
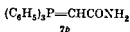
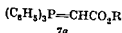
In the synthesis of olefins having electron-withdrawing groups on the α -carbon atom the reagent of choice is often the anion derived from a phosphonate ester. For example,



will react readily with cyclohexanone to form ethyl cyclohexylideneacetate. Reagents of this type are discussed on pp. 379–382.

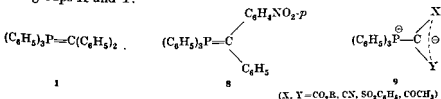
The preparatively important carbalkoxymethylene triphenylphosphoranes **7a** will also react with ketones but only under forcing conditions.^{34–37} However, the phosphorane **7a** reacts readily with cyclic

and methyl ketones in the presence of benzoic acid as a catalyst.³⁸ Reaction with aldehydes, on the other hand, occurs readily.^{3,39}



Carbalkoxymethylene triphenylphosphoranes (7a) are stable crystalline compounds which can be kept for a long time without decomposition. Participation of the ester group in charge delocalization is evident from the shift of the carbonyl band in the infrared to 6.15μ ,⁴⁰ as well as from the stability of the compounds. Carbamidomethylenetriphenylphosphorane (7b)⁴¹ and cyanomethylenetriphenylphosphorane (7c)⁴¹⁻⁴³ also belong to this group of stable phosphoranes.

Replacement of the second hydrogen atom in the methylene group by an electron-delocalizing substituent results in further decrease of the reactivity of the phosphoranes to such an extent that they may become unreactive even toward aldehydes. Examples of such phosphoranes are diphenylmethylenetriphenylphosphorane (1),⁸ 4-nitrobenzhydrylenetriphenylphosphorane (8),⁴⁴ and compounds of type 9,⁴⁵ whose ultraviolet spectra show that the negative charge is extensively delocalized into the two groups X and Y.



The methylene carbon atom may also be made part of a quasi-aromatic system with a resulting decrease in the carbanion character of the ylide. Cyclopentadienyliidenetriphenylphosphorane (10),^{46,47} for instance, is a yellow crystalline compound, m.p. $229-231^\circ$, stable to prolonged heating with concentrated aqueous or ethanolic potassium hydroxide. It does not react with benzophenone, fluorenone, or cyclohexanone on heating in

³⁸ Rüchardt, Eichler, and Panse, *Angew. Chem.*, **75**, 858 (1963).

³⁹ Isler, Gutmann, Montavon, Rügge, and Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

⁴⁰ Bestmann and Schulz, *Chem. Ber.*, **95**, 2921 (1962).

⁴¹ Trippett and Walker, *J. Chem. Soc.*, **1959**, 3674.

⁴² Novikov and Shvekhgeimer, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1959**, 2061

[*C.A.*, **55**, 13353g (1961)].

⁴³ Schiemenz and Engelhard, *Chem. Ber.*, **94**, 578 (1961).

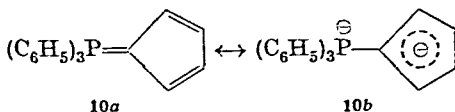
⁴⁴ Drefahl, Plotner, and Scholz, *Z. Chem.*, **1**, 93 (1961).

⁴⁵ Horner and Oediger, *Chem. Ber.*, **91**, 437 (1958).

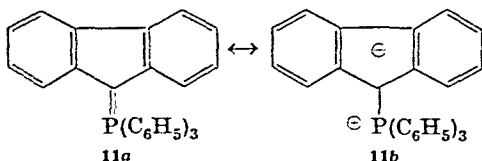
⁴⁶ Ramirez and Levy, *J. Org. Chem.*, **21**, 483 (1956).

⁴⁷ Ramirez and Levy, *J. Am. Chem. Soc.*, **79**, 67 (1957).

diethyl ether, chloroform, ethanol, or tetrahydrofuran for 120 hours. Reaction with benzaldehyde appears to occur, but no pure products could be isolated.



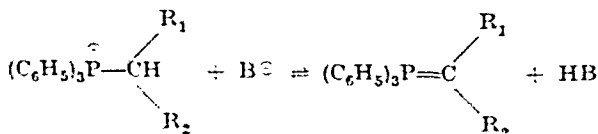
Fluorenylidetriphenylphosphorane (11)^{48,49} is considerably more reactive; it is hydrolyzed by ethanolic sodium hydroxide, and it undergoes the Wittig reaction with a number of aldehydes to give olefins. The dipole moment of 7.09 D points to the importance of resonance form 11b in the hybrid. Replacement of the phenyl groups on phosphorus by



alkyl groups in 11^{29,50} results in a marked increase in reactivity. Thus the hydrolysis of fluorenylidetrimethylphosphorane^{50,51} occurs readily under the influence of atmospheric moisture, and fluorenylidetributylphosphorane²⁹ may even be made to react with a number of ketones.

Preparation of Alkylidene Phosphoranes

The Wittig reagents are usually prepared by the action of bases on the easily accessible triphenylalkylphosphonium halides. Formation of



alkylidene phosphoranes by removal of a proton from the salt under the influence of base is a reversible reaction. The choice of conditions depends entirely on the nature of the desired ylide. The air- and moisture-sensitive phosphoranes of the first group have to be prepared in an anhydrous medium under an atmosphere of inert gas, employing

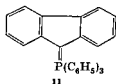
organometallic compounds as proton acceptors. In one method² an ether solution of phenyllithium or butyllithium is added under nitrogen to a suspension of 1 equivalent of the phosphonium salt in ether, tetrahydrofuran, or other suitable solvent. The reaction usually occurs in the cold, and formation of the alkylidene phosphoranes can be followed by the appearance of an intense yellow or red coloration.

A variation of this method consists in preparing the ylide in liquid ammonia with sodium amide as the base and then replacing ammonia by diethyl ether or tetrahydrofuran.⁵² Sodium amide has also been used in other solvents, such as benzene, diethyl ether, or tetrahydrofuran.⁵³

Alkylidene phosphoranes that do not react with a carboxamide function can also be prepared in dimethylformamide as the solvent; in these reactions, sodium acetylide has proved to be particularly useful as a base.^{54,55} Since many phosphonium salts can be readily prepared in dimethylformamide, the Wittig reaction can be carried out without isolation of the quaternary salt.

Another method for the preparation of alkylidene phosphoranes employs alkali metal alkoxides as proton acceptors, usually in the corresponding alcohol as solvent.³ The simplicity of this method is gaining more and more attention for it. The alkoxide procedure permits preparation of unstable ylides directly in the presence of carbonyl compounds, thus minimizing side reactions.

Since, unlike the reactive phosphoranes of the first group, the resonance-stabilized ylides of the second group are stable toward hydrolysis, they can be prepared by the action of alkali metal hydroxides on an aqueous solution of the phosphonium salt.^{39, 56} The phosphorane usually precipitates in crystalline form and can be dried in air. With sufficiently acidic phosphonium salts, weaker bases can also be used. For instance, fluorenylidene triphenylphosphorane (11)¹⁸ has been prepared by the action of ammonium hydroxide on the corresponding phosphonium salt, and *p*-nitrobenzylidenetriphenylphosphorane (12)⁵⁷ has been prepared



11



12

⁵² Wittig, Eggers, and Duffner, *Ann.*, **619**, 10 (1958).

⁵³ Wittig and Pommer, Ger. pat. 1,003,730 (to BASF) [*C. A.*, **53**, 16063c (1959)].

⁵⁴ Wittig and Pommer, Ger. pat. 954,247 (to BASF) [*C. A.*, **53**, 2279e (1959)].

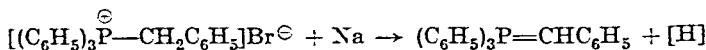
⁵⁵ Pommer, Wittig, and Sarnecki, Ger. pat. 1,026,745 (to BASF) [*C. A.*, **54**, 11074f (1960)].

⁵⁶ Gerecke, Ryser, and Zeller, Ger. pat. 1,125,922 (to Hoffman-La Roche), 1958, corresponds to U.S. pat. 2,912,467 [*C. A.*, **54**, 2254e (1960)].

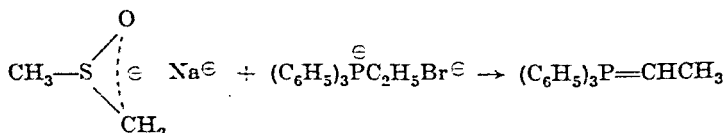
⁵⁷ Kröhnke, *Chem. Ber.*, **83**, 291 (1950).

using sodium carbonate as the base. Carbomethoxymethyltriphenylphosphonium bromide also reacts with sodium carbonate, whereas sodium hydroxide must be used in order to convert the less acidic carbomethoxymethyltricyclohexylphosphonium bromide to its ylide.²⁸ Triethylamine⁵⁸⁻⁶⁰ and pyridine^{58,60} have also been used for the preparation of resonance-stabilized alkylidene phosphoranes.

Other methods for the preparation of alkylidene phosphoranes from phosphonium salts are known. Hydrogen bromide can be eliminated from triphenylbenzylphosphonium bromide with metallic sodium.⁶¹

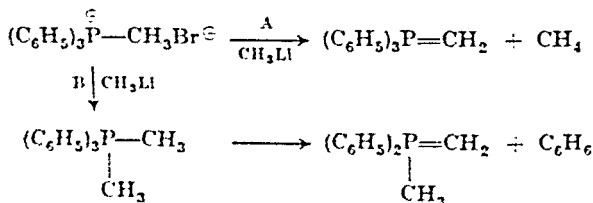


Ethylidenetriphenylphosphorane is obtained in very good yield by the action of methylsulfinyl carbanion on triphenylethylphosphonium bromide in dimethyl sulfoxide.^{62,63} Finally it should be mentioned that

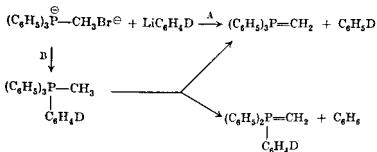


Coffmann and Marvel⁶⁴ were the first to prepare ylides by the organo-metallic route by allowing trityl sodium to react with triphenylalkylphosphonium salts.

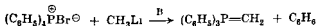
The mechanism of ylide formation by the interaction of organolithium compounds with phosphonium salts was the subject of an interesting study.⁶⁵ The organic base not only removes a proton from the α -carbon atom (path A) but also adds to a certain extent to phosphorus, forming a presumably pentavalent intermediate which then collapses into alkylidene-phosphorane and a hydrocarbon (path B). The formation of benzene.



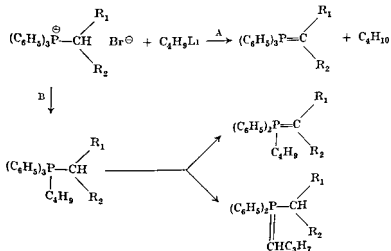
obtained in 20% yield, could take place only by path B. Similarly, interaction of triphenylmethylphosphonium bromide with *p*-deuteriophenyllithium gave benzene in addition to deuteriobenzene.



The reaction of tetraphenylphosphonium bromide with methyllithium must have proceeded via path B exclusively, since benzene was obtained in quantitative yield. Path A is ruled out in this reaction since the α -carbon atom does not carry a hydrogen atom.

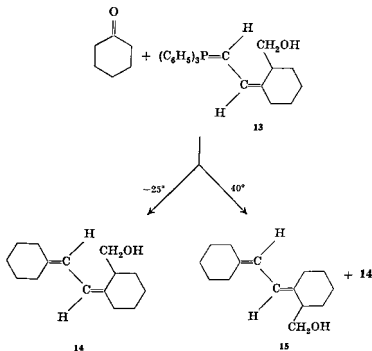


These results indicate that phenyllithium rather than butyllithium will be preferred for the organometallic preparation of ylides, since butyllithium may give rise to the formation of butylidene phosphoranes in addition to the desired ylide. It must be stressed, however, that



certain reactions proceed by path A exclusively. Thus the reaction of benzyltriphenylphosphonium bromide with methyllithium apparently

by the *cis-trans* isomerization of the partial allylic double bond which occurs more or less readily at room temperature. Thus the ylene 13 reacts with cyclohexanone at -25° with the almost exclusive formation of the expected *cis*-diene 14, whereas at $+40^{\circ}$ a 20% yield of the *trans* isomer 15 is also obtained.⁶⁹ In order to get pure isomers, it is therefore



necessary to work at low temperatures. This requirement poses no problem in view of the high reactivity of the allyldene phosphoranes

Hydroxyl groups in the ylide may be protected by conversion to acetals or tetrahydropyranyl ethers⁷⁰⁻⁷² Example 13 shows that this is not absolutely necessary provided sufficient base is present to convert the alcohol to alkoxide.

Side reactions in the preparation of alkylidene phosphoranes from phosphonium salts are very rare and can usually be avoided by suitable choice of conditions. In fact, complications are to be expected only if the ylide carries a substituent in the β -position to the phosphorus atom which

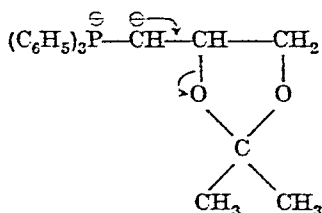
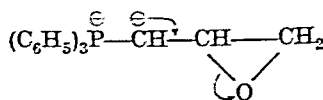
⁶⁹ Harrison and Lythgoe, *J. Chem. Soc.*, 1958, 843.

⁷⁰ Inhoffen, Bruckner, and Heas, *Chem. Ber.*, **88**, 1850 (1955).

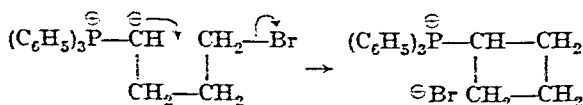
⁷¹ Bohlmann, Bornowski, and Herbat, *Chem. Ber.*, **93**, 1931 (1960).

⁷² Bohlmann and Ruhnke, *Chem. Ber.*, **93**, 1945 (1960).

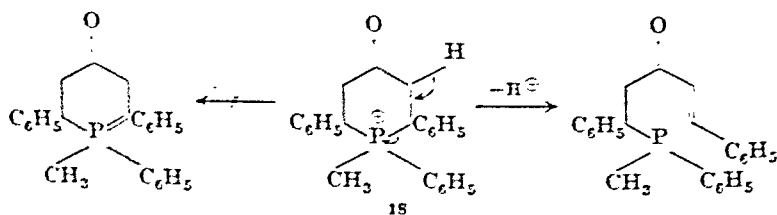
is prone to nucleophilic displacement, or if a proton in the β -position is so acidic that Hofmann elimination will be favored over ylide formation. Thus the ylides **16** and **17**⁷³ decompose very readily, as evidenced by the rapid disappearance of the color.

**16****17**

Halogen atoms also may undergo an intramolecular nucleophilic displacement, which in special cases leads to cyclic products.^{74,75}



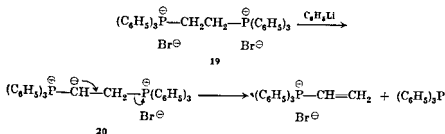
Attempts to prepare a heterocyclic phosphorus ylide from the phosphonium salt **18** were not successful; Hofmann elimination with ring opening occurred instead.⁷⁵ On the other hand, certain other cyclic



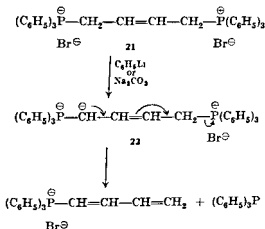
alkylidene phosphoranes can be prepared.⁷⁷

The bis-phosphonium salt **19** also undergoes Hofmann elimination under the influence of phenyllithium in ether with the formation of triphenylvinylphosphonium bromide and triphenylphosphine, the mono ylide **20**

being a probable intermediate.⁵²



The ylide **22**, a vinylog of **20**, also eliminates triphenylphosphine by a process involving the electrons of the central double bond.^{78,79}



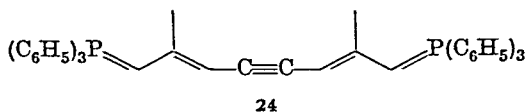
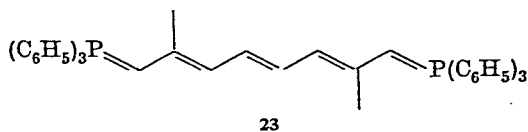
If such unstable alkylidene phosphoranes are encountered in the course of a Wittig reaction, it is necessary to carry out the condensation with carbonyl compounds very rapidly and, if possible, *in statu nascendi*. Best suited for this purpose is the alkoxide method which permits the addition of aldehydes or ketones before the ylide is prepared. Thus, if the bis-phosphonium salt **21** is treated with lithium ethoxide in ethanol in the presence of aldehydes,^{79a} decomposition of the mono ylide **22** is prevented and the normal products of the Wittig reaction are obtained.

⁷⁸ H. Burger, Doctoral Dissertation, Universität Tübingen, 1958.

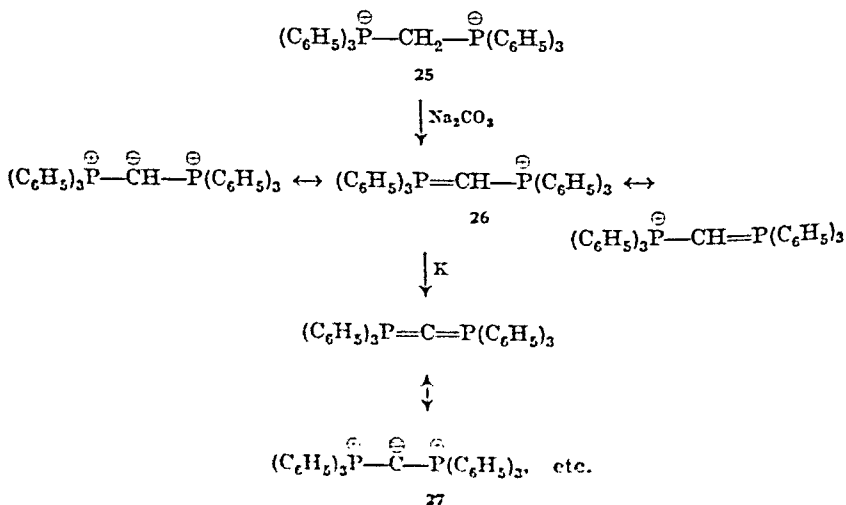
⁷⁹ Ford and Wilson, *J. Org. Chem.*, **26**, 1433 (1961).

^{79a} Heitman, Sperna Weiland, and Huismann, *Koninkl. Ned. Akad. Wetenschap., Proc., Ser. B*, **64**, 165 (1961) [*C.A.*, **55**, 17562f (1961)].

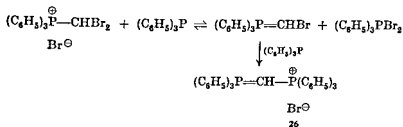
Bifunctional ylides with several central double bonds or with a central triple bond (23, 24) can be prepared without complication by the organo-metallic method, since the initially formed mono ylides are more stable than the mono ylide 22.⁸⁰



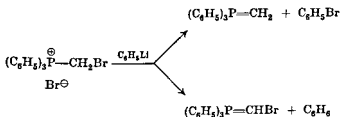
The interaction of bases with methylene bis(triphenylphosphonium bromide) (25)⁸¹ leads to interesting ylides in which the two positively charged phosphorus atoms are separated by only one carbon atom. On addition of aqueous sodium carbonate there is first obtained the colorless, resonance-stabilized mono ylide 26, which is then converted under the influence of metallic potassium in diglycol dimethyl ether to the stable yellow hexaphenylcarbodiphosphorane 27.



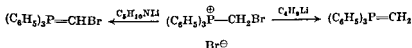
The same mono ylide **26** was obtained by the elimination of bromine from dibromomethyltriphenylphosphonium bromide with triphenylphosphine.⁸²



In the preparation of alkyldiene phosphoranes from α -haloalkylphosphonium salts and organometallic compounds the possibility of halogen-metal interchange reactions must also be taken into account.^{83,84}



Bromomethyltriphenylphosphonium bromide will react with butyllithium in ether with the exclusive formation of methylenetriphenylphosphorane, whereas with lithium piperidide no halogen-metal interchange takes place.⁸⁴



The interaction of bases with chloromethyltriphenylphosphonium halides leads to the formation of chloromethylenetriphenylphosphorane (28). Under the further influence of bases this compound undergoes an interesting rearrangement in which a chloride ion is lost and a phenyl group migrates from phosphorus to the methylene carbon atom.^{85,86}

⁸² Ramirez, Desai, and McKelvie, *J. Am. Chem. Soc.*, **84**, 1745 (1962).

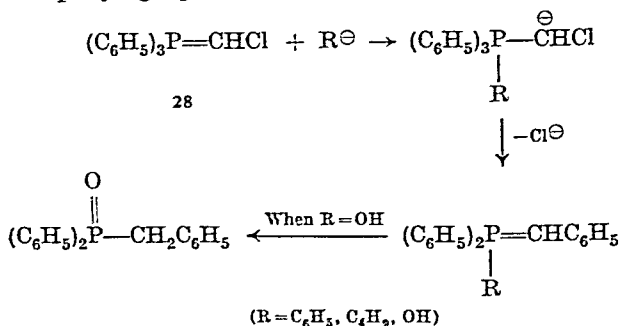
⁸³ Seyferth, Heeren, and Grim, *J. Org. Chem.*, **26**, 4783 (1961).

⁸⁴ Köbrich, *Angew. Chem.*, **74**, 33 (1962).

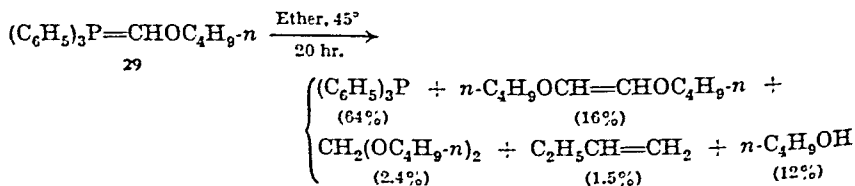
⁸⁵ Schlosser, *Angew. Chem.*, **74**, 291 (1962).

⁸⁶ Hellmann and Bader, *Tetrahedron Letters*, 1961, 724.

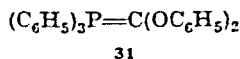
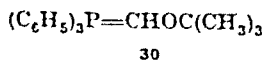
Although the mechanism is not entirely clear, it may be formulated as in the accompanying equations.⁶⁵



Methylene phosphoranes in which one hydrogen atom of the methylene group is replaced by an alkoxide group decompose in an even more complicated way. The autodecomposition of *n*-butoxymethylenetriphenylphosphorane (29) gave, in addition to triphenylphosphine as the main product, and depending on the conditions, varying amounts of 1,2-di-*n*-butoxyethylene, di-*n*-butoxymethane, 1-butene, and *n*-butanol.⁶⁷



The mechanism has not been elucidated, but it has been suggested that the phosphorane 29 decomposes initially into triphenylphosphine and *n*-butoxycarbene. *t*-Butoxymethylenetriphenylphosphorane (30) and diphenoxymethylenetriphenylphosphorane (31) decompose in an essentially analogous manner.⁶⁷

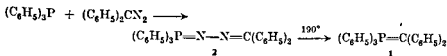


Even these phosphoranes, however, may be used in a Wittig reaction by operating at a sufficiently low temperature so that their rate of decomposition is slow.

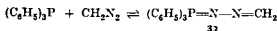
So far only methods for the preparation of alkylidene phosphoranes which use phosphonium salts as starting materials have been mentioned. There are, however, other theoretically very interesting ways of preparation which do not start with phosphonium salts. The first alkylidene

⁶⁷ Wittig and Bull, *Chem. Ber.*, 95, 2526 (1962).

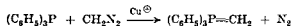
phosphorane **1** was obtained by the thermal decomposition of the phosphazine **2**.^{7,8} The applicability of this method remained limited, however,



since thermal elimination of nitrogen usually occurs at temperatures at which the phosphoranes are unstable. Even the similarly resonance-stabilized fluorenylidene triphenylphosphorane (**11**) could not be prepared by this route.⁸⁸ The action of diazomethane on triphenylphosphine in ethereal solution gives formaldehyde triphenylphosphazine (**32**),³ which at elevated temperatures decomposes into the starting materials.

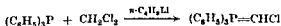


The preparation of methylenetriphenylphosphorane from diazomethane did, however, succeed under the catalytic influence of metal salts such as cuprous chloride⁸⁹ in the presence of triphenylphosphine.⁹⁰



Similarly other diazo compounds such as phenyldiazomethane, diazoacetic ester, or diazoacetophenone have been converted to the corresponding ylides. Since the ylides can undergo side reactions with excess diazo compound, it is best to generate them in the presence of carbonyl compounds if they are to be used for the preparation of olefins.

The addition of carbenes to triphenylphosphine, simultaneously discovered by Wittig,^{91,92} Speziale,^{93,94} Seyferth,^{95,96} and their co-workers, also leads to alkylidene phosphoranes which were used for the syntheses of monohalo- and 1,1-dihalo-olefins. The action of *n*-butyllithium on a solution of triphenylphosphine in methylene chloride at -60° , for instance, leads to chloromethylenetriphenylphosphorane.^{91,92,95,96}



⁸⁸ Horner and Lingnau, *Ann.*, **591**, 135 (1955).

⁸⁹ Wittig and Schwarzenbach, *Angew. Chem.*, **71**, 632 (1959). *Ann.*, **650**, 1 (1961).

⁹⁰ Wittig and Schlosser, *Tetrahedron*, **18**, 1023 (1962).

⁹¹ Wittig and Schlosser, *Angew. Chem.*, **72**, 324 (1960).

⁹² Wittig and Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

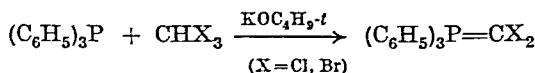
⁹³ Speziale, Marco, and Ratta, *J. Am. Chem. Soc.*, **82**, 1260 (1960).

⁹⁴ Speziale and Ratta, *J. Am. Chem. Soc.*, **84**, 854 (1962).

⁹⁵ Seyferth, Grim, and Read, *J. Am. Chem. Soc.*, **82**, 1510 (1960).

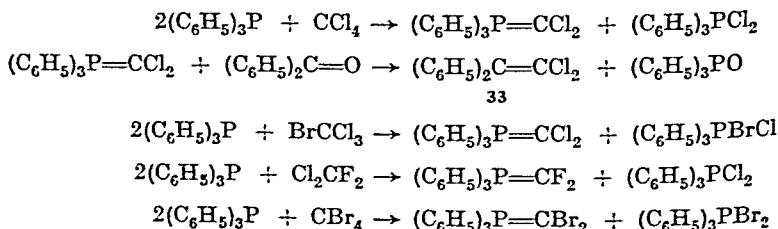
⁹⁶ Seyferth, Grim, and Read, *J. Am. Chem. Soc.*, **83**, 1617 (1961).

In an analogous manner dihalomethylene triphenylphosphoranes were prepared from triphenylphosphine, haloform, and potassium *t*-butoxide in heptane.^{93,94} The preparation of difluoromethylenetriphenylphos-



phorane⁹⁷ by a similar method could not be reproduced.⁹⁴

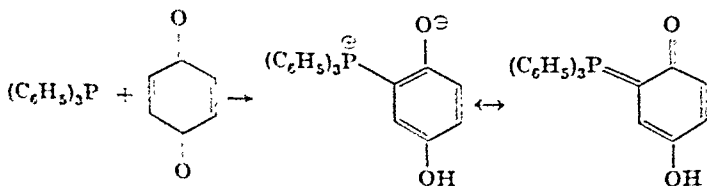
Dihalomethylene triphenylphosphoranes can also be prepared in good yields by the action of triphenylphosphine on tetrahalomethanes. Heating a mixture of triphenylphosphine, carbon tetrachloride, and benzophenone to 60° for 4 hours, for instance, gave 1,1-diphenyl-2,2-dichloroethylene (33) in 78% yield.^{82,98}



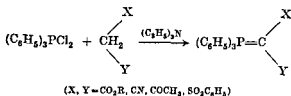
Similarly, tetrabromomethane reacts with triphenylphosphine in methylene chloride to give dibromomethylenetriphenylphosphorane, which was trapped with benzaldehyde to give β,β -dibromostyrene in 84% yield.⁸²



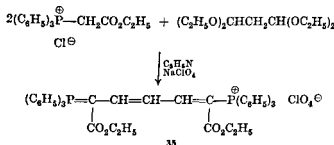
Benzoquinone and triphenylphosphine readily combine to give the yellow-green resonance-stabilized phosphorane 34.⁹⁹



Another method for the preparation of resonance-stabilized alkylidene phosphoranes uses triphenylphosphine dichloride as a starting material.⁴⁵

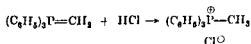


Finally, the phosphocyanine dye 35,¹⁰⁰ a resonance-stabilized phosphorane, may be considered to be a substituted vinyllog of the mono ylide 26.

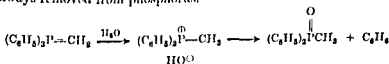


Reactions of Alkylidene Phosphoranes

Some of the reactions of the Wittig reagents reflect their markedly basic properties. All ylides react with acids to form phosphonium salts.¹



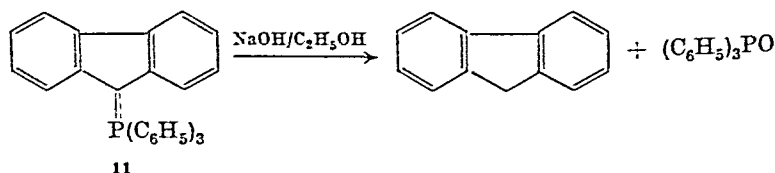
Similarly, hydrolysis¹ of unstable alkylidene phosphoranes gives phosphonium hydroxides which usually decompose irreversibly into a phosphine oxide and a hydrocarbon.¹⁰¹ The most electronegative group is always removed from phosphorus.



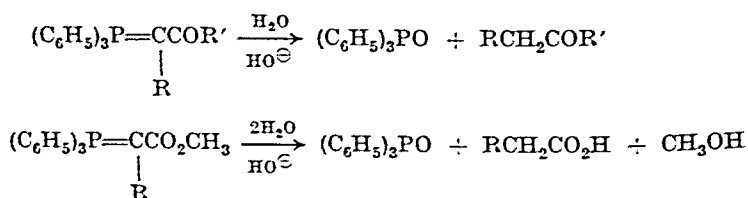
¹⁰⁰ Kukhtin, Kuzynov, and Voshchinskaya, *Dokl. Akad. Nauk SSSR*, **140**, 601 (1961).

¹⁰¹ Fenton and Ingold, *J. Chem. Soc.*, **1929**, 2342

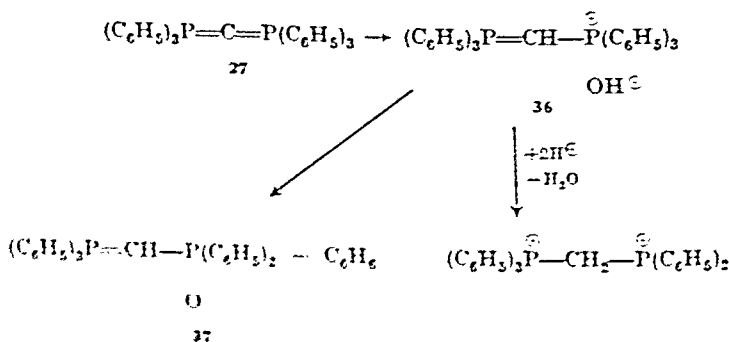
In order to hydrolyze resonance-stabilized alkylidene phosphoranes it is necessary to apply elevated temperatures and to use aqueous or alcoholic solutions of alkali metal hydroxides, as shown in the example of fluorenylidenetriphenylphosphorane (11).⁴⁹



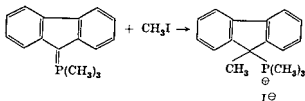
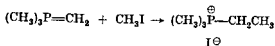
Hydrolysis of acylalkylidene triphenylphosphoranes^{31,32} gives ketones; of carbomethoxyalkylidene triphenylphosphoranes,⁴⁰ carboxylic acids. In



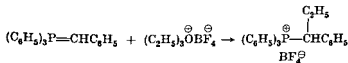
certain cases, phosphonium hydroxides are quite stable. Hexaphenylcarbodiphosphorane (27), for instance, dissolves readily in water to give a strong diacidic base (36) that can be titrated with hydrochloric acid. The elimination of benzene with the formation of a new ylene 37 which is stabilized by a phosphoryl group occurs only very slowly.⁵¹



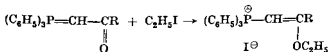
The addition of alkyl halides to alkylidene phosphoranes leads to phosphonium halides.^{51,102}



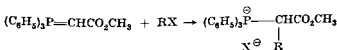
Similarly, trialkyloxonium fluoborates give the corresponding phosphonium fluoborates.^{102,103}



Resonance-stabilized ylides are not necessarily attacked on the α -carbon atom. Acylmethylene triphenylphosphoranes, for instance, are alkylated on oxygen.³¹



Carbomethoxymethylenetriphenylphosphorane, on the other hand, is alkylated on carbon.^{40,104}



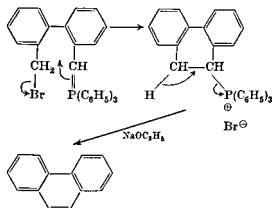
An electron-withdrawing group, R, will increase the acidity of the newly formed phosphonium salt relative to that of the unsubstituted one, and the salt therefore reacts with excess starting ylide by *trans* ylidation with

¹⁰² Wittig and Rieber, *Ann.*, 562, 177 (1949).

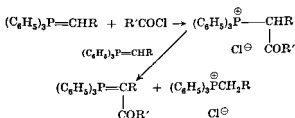
¹⁰³ Märkl, *Tetrahedron Letters*, 1962, 1027.

¹⁰⁴ Bestmann and Schulz, *Tetrahedron Letters*, 4, 5 (1960).

The postulation of carbene intermediates is not necessary since, as will be shown later, ylides are capable of adding to activated double bonds with the formation of cyclopropane derivatives. Phosphoranes containing halogen atoms can undergo an intramolecular carbon alkylation^{74,109} and may thus be used for the synthesis of cyclic compounds such as phenanthrene.¹⁰⁹

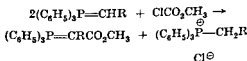


Alkylidene phosphoranes react readily with acid chlorides. The initially formed phosphonium salts undergo *trans* ylidation very easily owing to the strongly electron-withdrawing effect of the acyl group.^{32,41,58 110}



Strongly basic ylides may eliminate hydrogen chloride from acid chlorides containing activated α -hydrogen atoms (e.g., phenylacetyl chloride). The ketenes so formed react with the alkylidene phosphoranes to give allenes.³²

Chloroformic esters and alkylidene triphenylphosphoranes react to give carbalkoxymethylene triphenylphosphoranes.¹¹¹

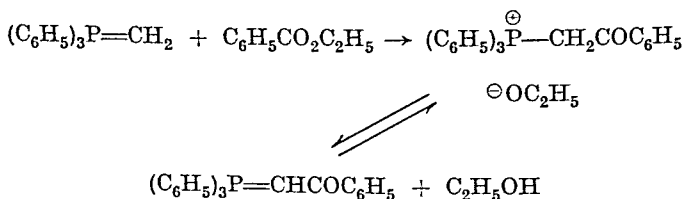


¹⁰⁰ Bestmann and Häberlein, *Z. Naturforsch.*, 17b, 787 (1962).

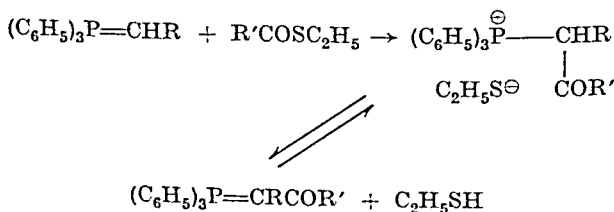
Bestmann, *Tetrahedron Letters*, 4, 7 (1960).

¹¹¹ Bestmann and Schulz, *Angew. Chem.*, **73**, 27 (1961).

In a reaction similar to that of acid chlorides, carboxylic esters react with alkylidene phosphoranes with the formation of phosphonium alkoxides.²

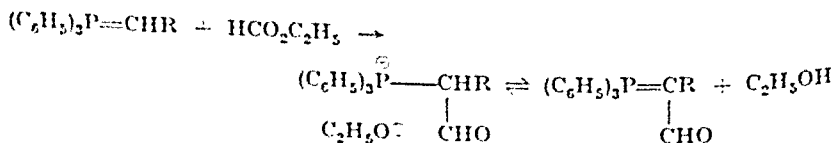


Using thiocarboxylic acid S-ethyl esters, a convenient method for the preparation of acylalkylidene triphenylphosphoranes was developed.^{32,112} Removal of the volatile mercaptan shifts the equilibrium from the initially formed phosphonium ethyl mercaptide completely to the side of the corresponding ylene. Compared with the acylation with acid



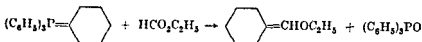
chlorides, this method has the advantage that the components may be used in a 1:1 ratio since deprotonation of the initially formed phosphonium salt is carried out by mercaptide ion and not by an excess of the starting ylene. In addition, the possibility of ketene formation is reduced, and, consequently, the yields are usually considerably higher.

With formic esters, which may be considered to contain both an aldehyde and an ester function, phosphoranes react to give different products depending on the conditions used. Adding an ylide to an excess of ethyl formate results in the normal ester reaction products, in this case formylethylidenetriphenylphosphorane.^{33,58}

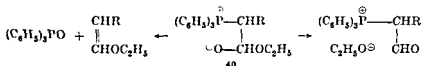


¹¹² Bestmann and Arnason, *Tetrahedron Letters*, 1961, 455.

Inverse addition, on the other hand, yields the products of a Wittig reaction, namely, an enol ether and triphenylphosphine oxide.¹¹³

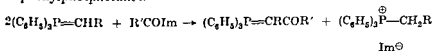


An explanation for these differing results may possibly be found in a solvation of the positively charged phosphorus by excess formic ester. In the first case, such a solvation might preclude the Wittig reaction by making a nucleophilic attack of the oxygen on phosphorus impossible; the zwitterion **40**, which is probably initially formed, therefore collapses in a different way. Support for this explanation is found in the fact that

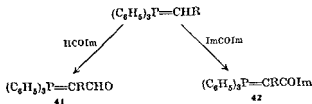


lithium bromide, which is known to shield phosphorus by complex formation,¹¹⁴ increases the yields in the above-mentioned reaction of alkylidene phosphoranes with normal esters³² in which a side reaction involving attack of the oxygen on phosphorus must also be expected.

The imidazolides, which are related to acid chlorides and esters, have been found to be particularly useful in the preparation of acylalkylidene triphenylphosphoranes.¹¹⁵



Using N-formylimidazole, the corresponding formylalkylidene triphenylphosphoranes (**41**) are obtained; with N,N'-carbonyldiimidazole, carbonylimidazolidoalkylidene triphenylphosphoranes (**42**)¹¹⁶ are formed.



¹¹³ Pommer and Wittig, Ger. pat. 1,047,763 (to BASF) (*Chem. Zentr.*, 1959, 13577).

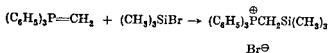
¹¹⁴ Bergelson and Shemyakin, *Tetrahedron*, **19**, 149 (1963).

¹¹⁵ Bestmann, Sommer, and Staab, *Angew. Chem.*, **74**, 293 (1962).

¹¹⁶ Staab and Sommer, *Angew. Chem.*, **74**, 294 (1962).

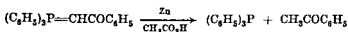
phenyldibromophosphine, diphenylbromophosphine,¹¹⁹ or triphenylphosphine dibromide.⁸²

Metalloidal, tin, and mercury halides undergo an interesting nucleophilic displacement of halide ion under the influence of ylides.¹²⁰⁻¹²² The products are phosphonium salts substituted on the α -carbon atom by metalloids, tin, or mercury.

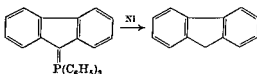


Alkylidene phosphoranes are also capable of cleaving silicon-silicon bonds; for instance, methylenetriphenylphosphorane reacts with octaphenylcyclotetrasilane with opening of the ring.¹²³

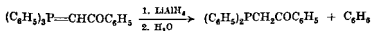
Metals may be used as reducing agents for ylides. Thus zinc in acetic acid converts acylmethylene triphenylphosphoranes to ketones and triphenylphosphine.⁵⁸



The same result is obtained with Raney nickel, but triphenylphosphine is unstable toward Raney nickel and cannot be isolated.¹²⁴



Reduction of ylides with lithium aluminum hydride takes a different course. One phenyl group is removed from phosphorus with the formation of benzene.¹²⁵



The reactive alkylidene phosphoranes are easily oxidized. They are so sensitive to oxygen that their preparation has to be carried out in an inert atmosphere. Oxidation leads, initially, to triphenylphosphine oxide and a carbonyl compound; the latter undergoes a Wittig reaction with

¹¹⁹ Seyferth and Brändle, *J. Am. Chem. Soc.*, **83**, 2035 (1961).

¹²⁰ Grim and Seyferth, *Chem. Ind. (London)*, 1959, 849.

¹²¹ Seyferth, *Angew. Chem.*, **72**, 36 (1960).

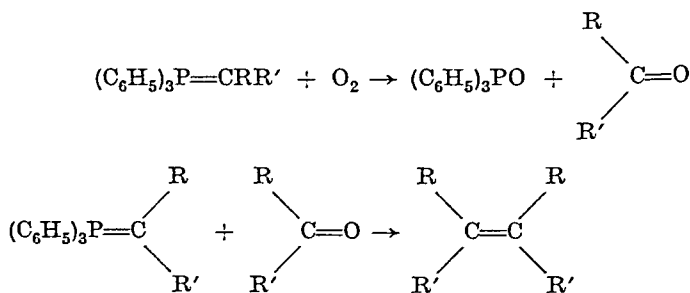
¹²² Seyferth and Grim, *J. Am. Chem. Soc.*, **83**, 1610 (1961).

¹²³ Gitman and Tomasi, *J. Org. Chem.*, **27**, 3647 (1962).

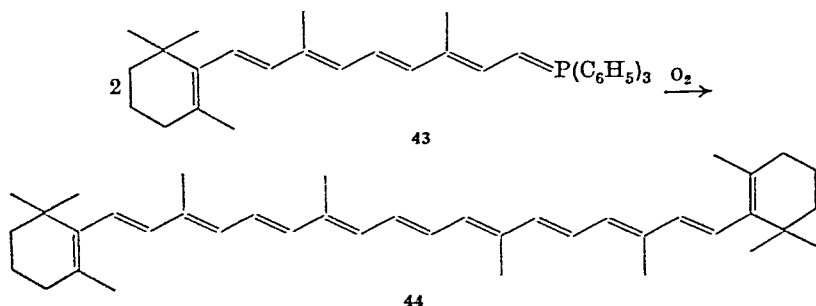
¹²⁴ Schönberg, Brosowski, and Singer, *Chem. Ber.*, **95**, 2984 (1962).

¹²⁵ Saunders and Burchman, *Tetrahedron Letters*, **1**, 8 (1959).

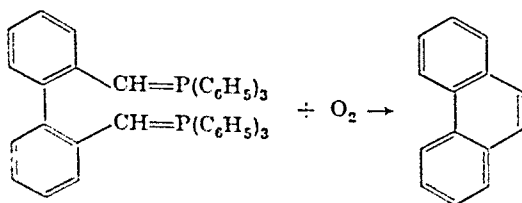
unoxidized ylide to form the symmetrical olefin in which both halves come from the alkylidene phosphorane.^{126,127}



By this method, vitamin A was converted to β -carotene (44) via *axer-*ophthylenetriphenylphosphorane (43).¹²⁸

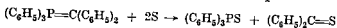


Oxidation of bifunctional ylides may lead to ring closure¹²⁷ as, for instance, in a synthesis of phenanthrene. Peracetic acid can be used

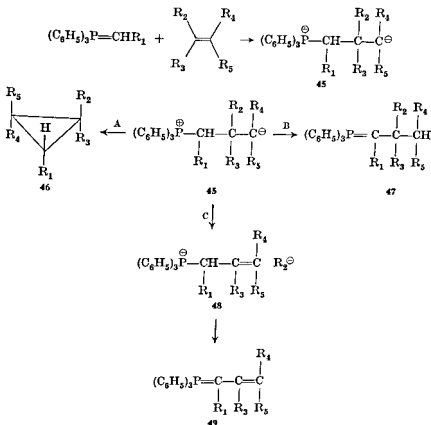


instead of oxygen as the oxidizing agent.¹²⁹ This reagent is also capable of oxidizing the resonance-stabilized ylides such as acylalkylidene and carbalkoxyalkylidene triphenylphosphoranes.

Staudinger found that, in analogy to its oxidation, diphenylmethylenetriphenylphosphorane reacts with elemental sulfur to give triphenylphosphine sulfide and thiobenzophenone. Because of the low reactivity of the phosphorane, a further reaction did not take place.⁸



In their capacity as nucleophiles, alkylidene phosphoranes can add to activated double bonds. Depending on the nature of the substituent, the initially formed zwitterion 45 can stabilize itself in three different ways.



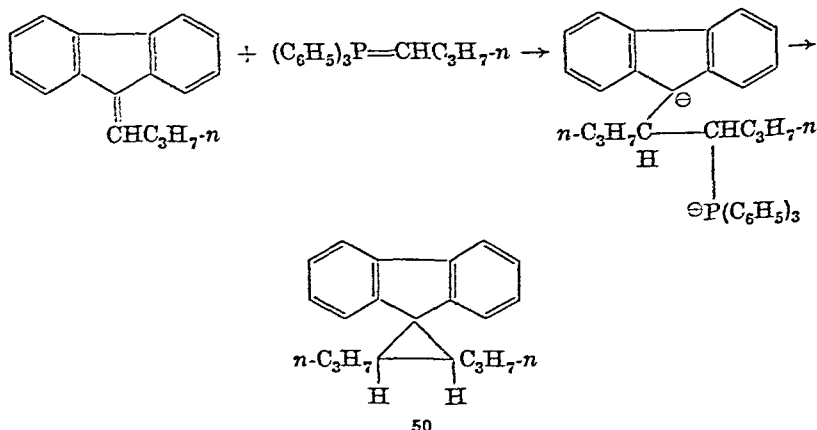
Formation of a cyclopropane derivative 46^{130 131} by elimination of triphenylphosphine (path A) is preferred if R₁ is a group which is not electron-withdrawing, e.g., hydrogen or alkyl.¹³² This is illustrated by

¹³⁰ Meechoulam and Sondheimer, *J. Am. Chem. Soc.*, **80**, 4386 (1958).

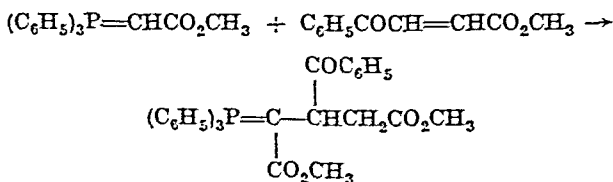
¹³¹ Freeman, *Chem. Ind. (London)*, 1959, 1254.

¹³² Bestmann and Seng, *Angew. Chem.*, **74**, 154 (1962).

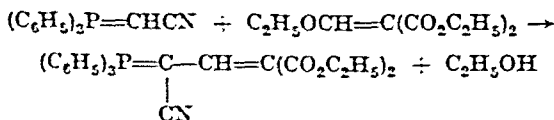
the reaction of 9-*n*-butylidene fluorene with *n*-butylidenetriphenylphosphorane, which yields the spiro compound 50.¹²⁰



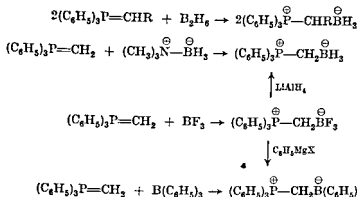
Michael addition of the alkylidene phosphorane to the double bond to form the new ylide 47 (path B) occurs preferentially if R_1 is an electron-withdrawing group capable of resonance interaction.¹³²



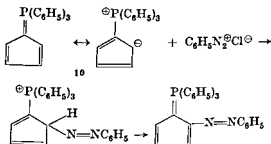
Path C is possible only if R_2 or R_3 are substituents capable of forming stable anions such as ethoxide or cyanide.¹²³



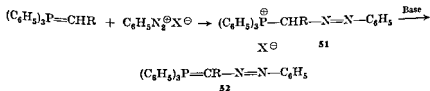
As expected, the Wittig reagents add to the electrophilic derivatives of trivalent boron, such as boron hydrides,^{134,135} boron halides,^{120,121,136} and triphenylboron.¹²⁶⁻¹²⁸



The reactions of alkylidene phosphoranes with a number of diazo compounds and diazonium salts are also of interest. Even the relatively unreactive cyclopentadienyldenetriphenylphosphorane (10) is readily attacked by benzenediazonium chloride. Strikingly, addition does not occur on the ylide carbon but in the 2-position, giving rise to the longest possible conjugated system.¹³⁹⁻¹⁴¹ The other resonance-stabilized Wittig



reagents are attacked by diazonium salts in the normal fashion on the α -carbon atom.^{142,143} The arylazoalkylphosphonium salts 51 so obtained can be converted with bases to arylazoalkylidene triphenylphosphoranes (52).



¹³⁹ Ramirez and Levy, *J. Org. Chem.*, **21**, 1333 (1956).

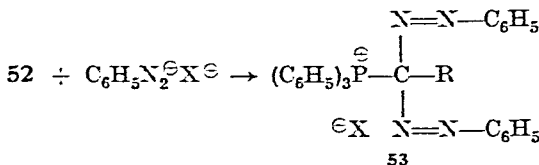
¹⁴⁰ Ramirez and Levy, *J. Am. Chem. Soc.*, **79**, 6167 (1957).

¹⁴¹ Ramirez and Levy, *J. Org. Chem.*, **23**, 2035 (1958).

¹⁴² Märkl, *Tetrahedron Letters*, 1961, 807.

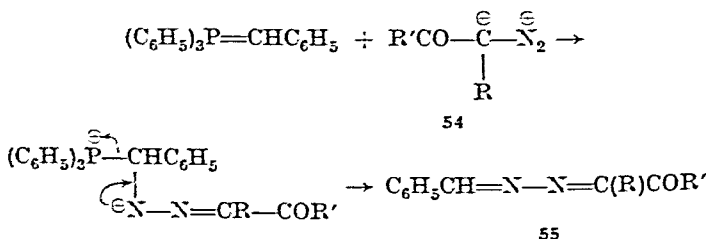
¹⁴³ Märkl, *Z. Naturforsch.*, **17b**, 782 (1962).

Strongly basic ylides (e.g., $R = C_6H_5$) furnish arylazoalkylidene phosphoranes (52) by *trans* ylidation without the addition of bases. Further reaction leads to the formation of bis-arylazoalkylphosphonium salts (53).

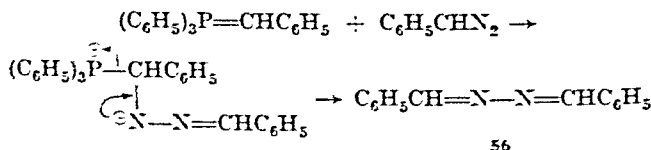


If $R = CO_2H$, subsequent elimination of carbon dioxide and hydrogen halide leads to bis-azoarylmethylene triphenylphosphoranes.¹⁴³

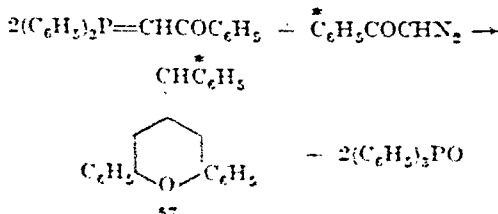
From benzylidenetriphenylphosphorane and aliphatic diazo compounds of structure 54, mixed azines 55 are formed.¹⁴⁴



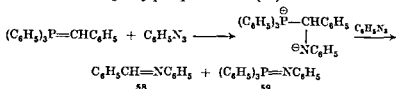
The same phosphorane reacts with phenyldiazomethane in a similar fashion to give benzalazine (56).⁹⁰



An unexpected result was obtained in the interaction of diazoacetophenone with benzoylmethylenetriphenylphosphorane to give the heterocyclic product 57. The only fact pertaining to the mechanism of this reaction is that the benzylidene group of the pyran derivative 57 is derived from the diazo compound.^{145,146}



The reaction of benzylidenetriphenylphosphorane with phenyl azide resembles that with diazo compounds.¹⁴⁷ The triphenylphosphine, which is formed in addition to benzylideneaniline (58), reacts with excess phenyl azide to furnish tetraphenylphosphine imide (59).



Of the further reactions of alkylidene phosphoranes, only those with carbonium and nitrilium salts will be mentioned.¹⁰³ In both cases nucleophilic attack by the ylide occurs on the carbon atom with the initial formation of substituted phosphonium salts, which may react further with bases.

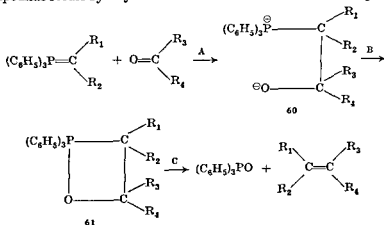
The preparatively most important aspect of the alkylidene phosphoranes is without doubt their reaction with carbonyl compounds to form olefins. The details of the Wittig reaction are discussed in the next section.

MECHANISM AND STEREOCHEMISTRY

Mechanism

Definitive kinetic studies of reactions of unstabilized alkylidene phosphoranes have not yet been made. In fact, it is not possible at present to make a final statement about the mechanism of the Wittig reaction. Using the available facts, it is possible, however, to outline the path of this complex reaction.

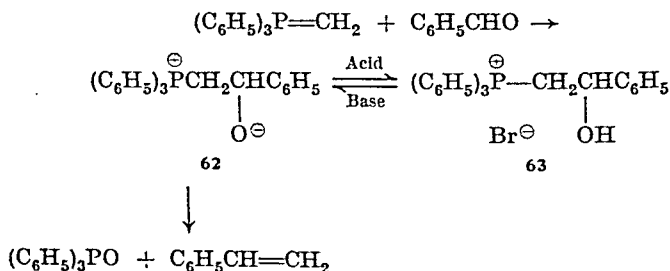
Olefin formation from alkylidene triphenylphosphoranes and carbonyl compounds occurs by way of the intermediates shown in the accompanying



¹⁴⁷ Hoffmann, *Chem. Ber.*, **95**, 2563 (1962).

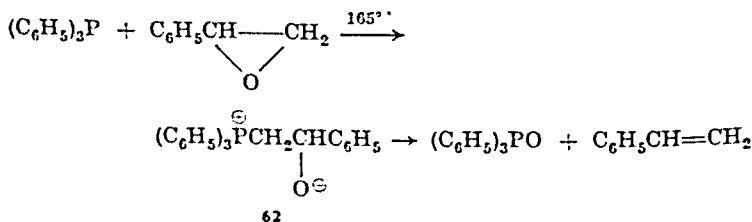
formulation. In the first step, nucleophilic addition of the alkylidene phosphorane in its ylide form to the polarized carbonyl group gives the phosphonium betaine **60**. As a consequence of the great affinity of phosphorus for oxygen and the possibility of expanding the valence shell of phosphorus to 10 electrons, a P—O bond is formed next, giving rise to the four-membered ring compound **61**, which then collapses into triphenylphosphine oxide and an olefin.

Experimental proof for the formation of a zwitterion in step A of the reaction was obtained from the interaction of methylenetriphenylphosphorane with benzaldehyde.² The zwitterion **62** is stable at room temperature and may be characterized as its hydrobromide **63**. The

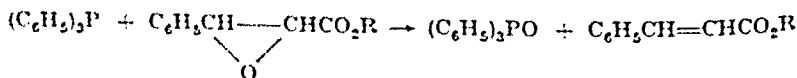


action of phenyllithium on the β -hydroxyphosphonium salt **63** regenerates **62**, which must be heated to 65° for an extended period in order to effect decomposition into triphenylphosphine oxide and styrene.

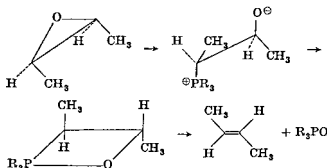
Initial formation of **62** has also been postulated for the reaction of triphenylphosphine with styrene oxide.³ Since ring opening of the epoxide requires a temperature of 165°, the reaction proceeds directly to styrene and triphenylphosphine oxide.



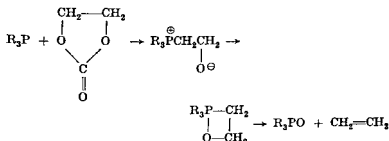
This is a general method for the conversion of epoxides to olefins. For example, cinnamic ester is obtained in 82% yield from phenylglycidic ester.



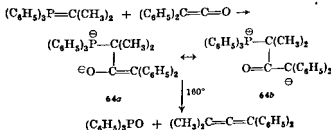
A stereochemical investigation of this deoxygenation reaction confirmed the mechanism proposed.¹⁴⁸ It was found that tributylphosphine reacts with *cis*-2-butene epoxide to form mainly *trans*-2-butene, whereas *trans*-2-butene epoxide gives mainly *cis*-2-butene.



An ionic intermediate has also been proposed for the reaction of cyclic carbonates with phosphines.¹⁴⁹



The isolation of unusually stable intermediates in a Wittig reaction has been reported recently.¹⁵⁰ Interaction of diphenylketene with isopropylidenetriphenylphosphorane gave a pale yellow crystalline compound, **64**, which cleaved to triphenylphosphine oxide and 1,1-dimethyl-3,3-diphenylallene only at temperatures above its melting point (140°). Hydrogen

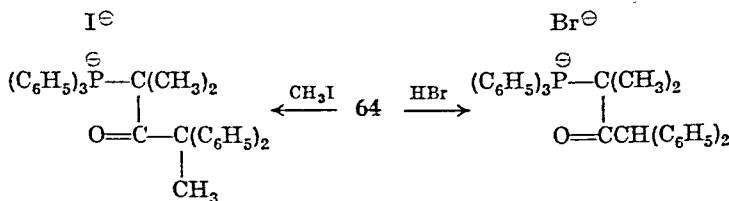


¹⁴⁸ Boskin and Denney, *Chem. Ind. (London)*, 1959, 330.

¹⁴⁹ Keough and Grayson, *J. Org. Chem.*, 27, 1817 (1962).

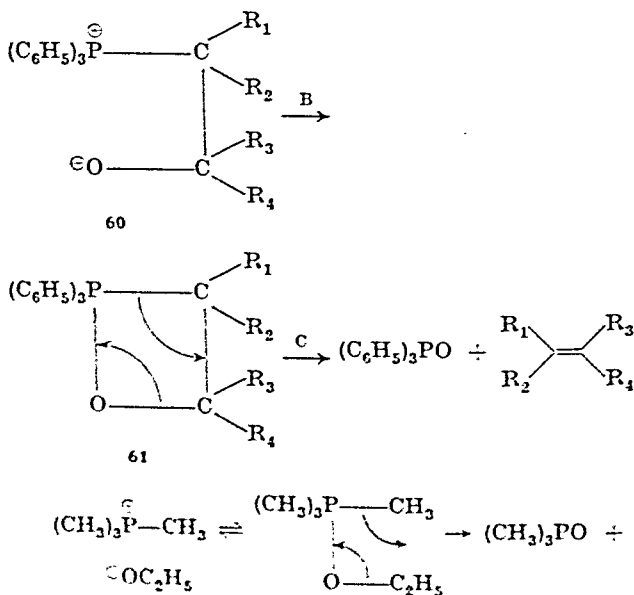
¹⁵⁰ Wittig and Haag, *Chem. Ber.*, 96, 1535 (1963).

bromide and methyl iodide attack compound 64 on carbon. In view of the relatively small dipole moment of 4.34 D, it cannot be said with certainty



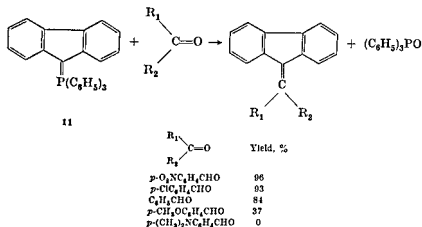
whether 64 has the structure of a zwitterion or that of a four-membered cyclic compound like 61.

The final step C of the Wittig reaction, *cis* elimination of triphenylphosphine oxide by way of the four-membered ring compound 61, is formally related to the decomposition of a phosphonium alkoxide into a phosphine oxide and a hydrocarbon.⁶⁷



Since it has never been observed that step C is the slowest and, therefore, the rate-determining step in a Wittig reaction, it cannot be decided at the present moment whether the four-membered ring compound 61 with a pentavalent phosphorus atom is actually an intermediate or a transition state. Depending on the reactants, however, either step A or B may become rate-determining. Studies of the interaction of fluorenylidene

phosphoranes with a number of substituted carbonyl compounds showed that, with resonance-stabilized phosphoranes, the first step, formation of a betaine, is rate-determining.^{29,49,50} Introduction of electron-withdrawing substituents into the benzaldehyde molecule resulted in an increased rate of reaction with fluorenylidetriphenylphosphorane (**11**). The reverse was true with electron-releasing substituents. No reaction

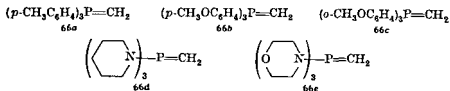


was observed with ketones such as acetone, benzophenone, 4,4'-dinitrobenzophenone, and fluorenone, but 2,4,7-trinitrofluorenone and the phosphorane **11** gave the corresponding olefin in quantitative yield.

A characteristic feature of resonance-stabilized phosphoranes, for which addition of the ylide to the carbonyl group is the critical step, is that replacement of the phenyl groups by alkyl groups facilitates formation of olefins. This is the result of the fact that electron-releasing groups on phosphorus result in a larger contribution to the ground state of the more reactive ylide form. Replacement of the phenyl groups in **11** by *n*-butyl groups does, indeed, give rise to a considerably more reactive phosphorane,²⁹ which under otherwise equal conditions gives almost quantitative yields of olefins with all the benzaldehyde derivatives mentioned above. In addition, it will react with a number of ketones which are completely unreactive toward the triphenyl derivative **11**. Thus good yields of olefins are obtained with 4,4'-dinitrobenzophenone as well as with *m*- and *p*-nitroacetophenone; the unsubstituted ketones will not react. Replacement of phenyl groups on phosphorus by alkyl groups such as methyl^{150,151} or cyclohexyl²⁸ has a favorable effect on the yields of the Wittig reaction of other resonance-stabilized alkylidene phosphoranes

¹⁵¹ Trippett and Walker, *Chem. Ind. (London)*, 1960, 933.

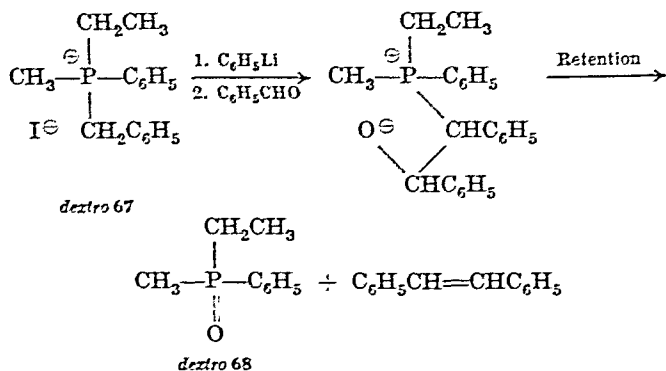
considerably decrease the activation energy for step A, it was observed that betaine formation was very rapid for each compound. The subsequent decomposition of the betaine by steps B and C, however, was more difficult in all examples and in some did not occur at all.



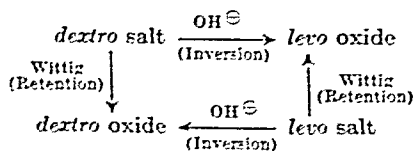
Since the polarity of the carbonyl group is of little consequence when the second step of the Wittig reaction is rate-determining, differently substituted aldehydes or ketones will usually give olefins in about the same yields. It is striking, furthermore, that the reactive phosphoranes, unlike the resonance-stabilized phosphoranes, react more readily with benzophenone than with benzaldehyde. Nucleophilic attack on benzaldehyde will in each case be easier than on the less reactive benzophenone and, consequently, reaction with the aldehyde will be preferred by the phosphoranes of low reactivity where the first step of the Wittig reaction requires the larger activation energy. However, introduction of phenyl groups on the β -carbon atom will facilitate the decomposition of the betaine into phosphine oxide and olefin (i.e., the rate-determining step with the reactive phosphoranes), and this will result in a more rapid collapse of the benzophenone adduct as compared with the benzaldehyde adduct. In general, it may be said that, whenever reaction of an ylide with benzophenone is faster than with benzaldehyde, the second step of the reaction, the decomposition of the betaine, is rate-determining. This explains why a number of resonance-stabilized alkylidene phosphoranes will react exclusively with aldehydes but not with benzophenone, whereas some of the reactive phosphoranes will interact readily with benzophenone but not with benzaldehyde. It also makes clear why betaines can usually be isolated only when benzaldehyde is used as the carbonyl component, whereas the benzophenone adducts as a rule are much less stable. Only from the methylene phosphoranes 66d and 66e was it possible to isolate adducts with benzophenone, since decomposition of the betaine is rendered extremely difficult as a consequence of the high electron density on phosphorus;¹⁵⁵ but even these adducts are less stable than the corresponding benzaldehyde adducts, which cannot be decomposed into olefin and phosphine oxide. The marked stability of the ketene adduct 64 is probably due to its stabilization by resonance.

Stereochemistry

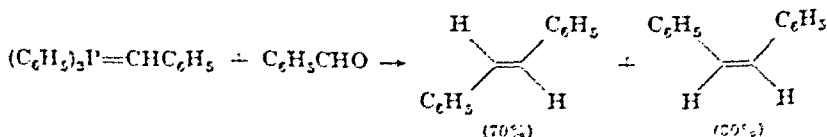
Experiments with the optically active phosphonium salts **67** showed that the Wittig reaction takes place with retention of configuration on phosphorus.^{156,157}



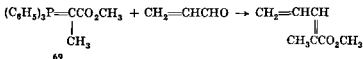
The same phosphine oxide, *dextro* **68**, is formed with inversion from the phosphonium salt, *levo* **67**, under the influence of alkali.



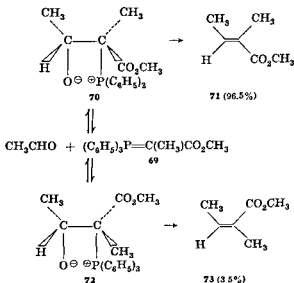
If the ylide and carbonyl components are unsymmetrically substituted, a mixture of *cis* and *trans* olefins is usually obtained. As a rule, the *trans* olefin predominates, as illustrated by the reaction of benzylidene-triphenylphosphorane with benzaldehyde which leads to a mixture containing 70% *trans*- and 30% *cis*-stilbene.² However, exclusive



predominance of the *cis* isomer.¹⁵⁹⁻¹⁶¹ Strikingly, the *trans* isomer is always formed predominantly or exclusively if resonance-stabilized alkylidene phosphoranes are used. Thus almost pure *trans* olefins were obtained by using cyanomethylenetriphenylphosphorane^{42,43} and carbomethoxymethylenetriphenylphosphorane^{39,162,163} as well as their derivatives.^{40,111,117,164} The observation that carbomethoxyethylidenetriphenylphosphorane (69) gives the pure *trans* compound with acrolein led to the systematic investigation of this reaction.¹⁶⁴



By means of the Wittig reaction, methyl 2-methyl-2-butenolate was prepared in two different ways. The ylide 69 and acetaldehyde furnished almost exclusively methyl tiglate (71), i.e., the *trans* isomer. Methyl pyruvate and ethylidenetriphenylphosphorane gave a mixture of isomers that contained 32% of the *cis* compound, methyl angelate (73).¹⁶⁴ In



¹³⁰ Wailes, *Chem. Ind. (London)*, 1958, 1086.

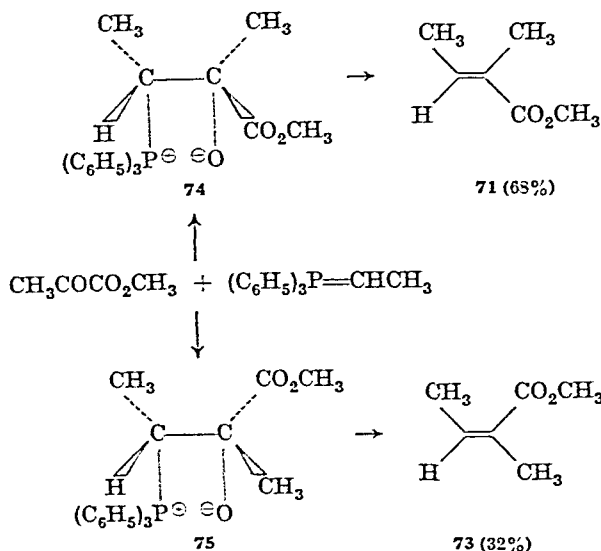
¹⁶⁰ Bohlmann, Inhoffen, and Herbat, *Chem. Ber.*, **90**, 1661 (1957).

¹⁴¹ Truscheit and Eiter, *Ann.*, 658, 65 (1962).

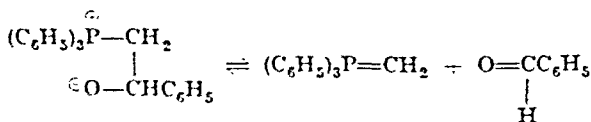
¹⁸² Novikov and Shvekhgeimer, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 1960, 673 [*C.A.*, 4, 22474h (1960)]

¹²³ Kucherov, Kovalev, Kogan, and Yanovskaya, *Dokl. Akad. Nauk SSSR*, **138**, 1115 (1961) [*C.A.*, **55**, 24560 (1961)].

¹⁶⁴ House and Rasmussen, *J. Org. Chem.*, **26**, 4278 (1961).



order to rationalize the observed isomer distributions, one may assume that the resonance-stabilized phosphorane 69 is in equilibrium with the two betaines 70 and 72. Here the first and, for the unreactive phosphoranes, slowest step will probably be reversible, so that the reaction may proceed predominantly by way of the sterically less hindered betaine 70, thus leading to the *trans* olefin. While such an interpretation of the isomer distribution from the stabilized ylide 69 seems reasonably satisfactory, the products formed from the reactive ethylenephosphorane are harder to rationalize. Decomposition of the betaines derived from reactive phosphoranes to starting materials was originally thought not to occur.¹⁵⁵ More recent studies, however, provide convincing evidence that benzaldehyde is formed from a simple betaine under mild conditions.¹⁶⁵

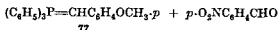
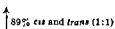
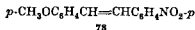
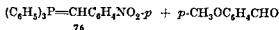


Thus it seems that a full understanding of the isomer distributions outlined above must await further research.

Another example of the differences in isomer distributions in the Wittig reaction is the preparation of 4-nitro-4'-methoxystilbene (78) by two

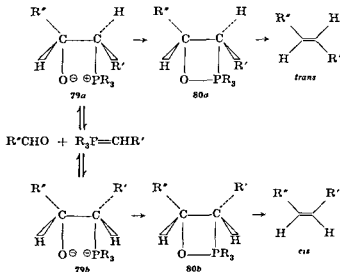
¹⁶⁵ Fieser, Hudson, and Salvadori, *Helv. Chim. Acta*, **46**, 1560 (1963).

methods.¹⁶⁶ Reaction of the resonance-stabilized *p*-nitrobenzylidene-phosphorane (76) with the relatively unreactive anisaldehyde leads to the



exclusive formation of the *trans* compound 78. The less stable, more reactive *p*-methoxybenzylidenephosphorane (77), on the other hand, reacts with the extremely reactive *p*-nitrobenzaldehyde to give a mixture of the *cis*- and *trans*-stilbenes 78 in the ratio of 1:1.

In the reactions of resonance-stabilized alkylidene phosphoranes with carbonyl compounds, the isomer ratio may be shifted further in favor of the *trans* products if the stability of the initially formed betaines 79*a* and 79*b* is increased, thus preventing further reaction before equilibrium has been reached. This was accomplished by substituting cyclohexyl groups for the phenyl groups on phosphorus.²⁸ The phosphorus is thus rendered less electrophilic, and the conversion of 79 to the end products by way of the four-membered ring compound 80 becomes more difficult. If the rate



¹⁶⁶ Ketchan, Jambotkar, and Martinelli, *J. Org. Chem.*, **27**, 4666 (1962).

of conversion of **79** to **80** is so rapid that the equilibrium $79a \rightleftharpoons 79b$ cannot be established, considerable amounts of *cis* olefins will be formed in addition to the *trans* compounds. If, on the other hand, establishment of the equilibrium is possible, the betaine **79a** leading to the *trans* isomer will be energetically favored to a large extent.

An effort to account for the predominance of *trans* compounds from resonance-stabilized phosphoranes has been made by postulating a nucleophilic attack on the phosphorus atom by the oxygen of the carbonyl component as the first step in such reactions.¹¹⁴ Other studies, however, indicate that the primary step is probably nucleophilic attack by the ylide carbon atom on the carbonyl carbon atom.^{167,168} In addition, substitution of phenyl groups on the phosphorus atom by cyclohexyl groups²⁸ leads not only to an increased yield of *trans* olefins but also to an increase of the total yield. Electron-releasing groups on phosphorus would be expected to impede rather than to facilitate the nucleophilic attack of the carbonyl oxygen on the phosphorus atom.

Studies have also been reported which indicate that reactive phosphoranes with aldehydes tend to give increased amounts of *cis* isomers in the products when the reaction is carried out in the presence of Lewis bases.^{114,169-172}

SCOPE AND LIMITATIONS

In the few years since the discovery of the Wittig reaction, many olefins have been synthesized by this method. The reaction is not limited to simple alkyl- or aryl-substituted ethylene derivatives but is also applicable to the synthesis of α,β -unsaturated carbonyl compounds and carboxylic esters as well as vinyl halides and vinyl ethers. The large number of natural products prepared by the Wittig reaction speaks for the importance that this olefin synthesis has attained in a short period.

Alkyl-Substituted Olefins

The Wittig reaction is especially valuable for the introduction of exocyclic double bonds and is the only method for converting a cyclic

¹⁴⁷ Goetz, Nerdel, and Michaelis, *Naturwissenschaften*, **14**, 496 (1963).

¹⁴⁸ Speriale and Ratts, *J. Org. Chem.*, **28**, 465 (1963).

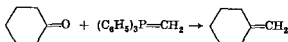
¹⁴⁹ Bergelson, Vaver, Barsukov, and Shemyakin, *Dokl. Akad. Nauk SSSR*, **143**, 111 (1962) [*C.A.*, **57**, 7298e (1962)].

¹⁵⁰ Bergelson, Vaver, Kovtun, Senyavina, and Shemyakin, *Zh. Obshch. Khim.*, **32**, 1892 (1962) [*C.A.*, **58**, 4415g (1963)].

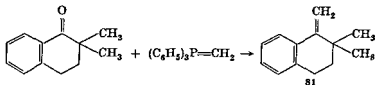
¹⁵¹ Bergelson, Vaver, and Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1960, 1960 [*C.A.*, **55**, 14294c (1961)].

¹⁵² Bergelson, Vaver, and Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1951, 729 [*C.A.*, **55**, 22196c (1961)].

ketone to the corresponding exocyclic olefin. The Grignard method is well known to give practically only the endocyclic isomer (Saytzeff rule). For example, cyclohexanone and methylenetriphenylphosphorane give methylenecyclohexane.²

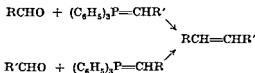


Similarly a whole series of methylenesteroids has been synthesized, and a methylene group has been successfully introduced into the vitamin D₂ skeleton. Recently methylenecycloheptane and methylenecyclo-octane have been prepared by this method,¹⁷³ as were derivatives of methylenedihydronaphthalene and methylenetetralin.¹⁷⁴ 1-Methylene-2,2-dimethyltetralin (81), for instance, was obtained in 83% yield.



Catalytic hydrogenation of the methylene compounds permits the conversion $>\text{C}=\text{O} \rightarrow >\text{CHCH}_3$.¹⁷⁵⁻¹⁷⁷

The synthesis of 1,2-disubstituted ethylene derivatives from aldehydes and monosubstituted methylene triphenylphosphoranes can be effected in two ways.



As a rule, mixtures of *cis* and *trans* olefins are formed in these reactions, for instance, in the synthesis of 1,1,1-triphenyl-3-pentene (82) from β,β,β -triphenylpropionaldehyde and ethyldenetriphenylphosphorane.¹⁷⁸



Unsaturated aldehydes can also be used. Propargylaldehyde, for instance, reacts with *n*-dodecylidenetriphenylphosphorane to give pentadec-3-en-1-yne (83).¹⁵⁹ The strikingly large amount of *cis* compound

¹⁷³ Schriesheim, Müller, and Rowe, *J. Am. Chem. Soc.*, **84**, 3164 (1962).

¹⁷⁴ Wittig, Reppe, and Eicher, *Ann.*, **643**, 47 (1961).

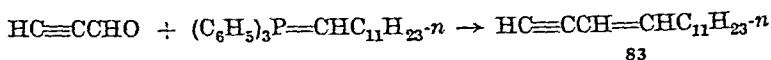
¹⁷⁵ Chadha and Rapoport, *J. Am. Chem. Soc.*, **79**, 5730 (1957).

¹⁷⁶ Büchi and MacLeod, *J. Am. Chem. Soc.*, **84**, 3205 (1962).

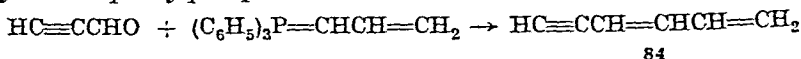
¹⁷⁷ DeGraw and Bonner, *Tetrahedron*, **18**, 1311 (1962).

¹⁷⁸ Wittig and Wittenberg, *Ann.*, **606**, 1 (1957).

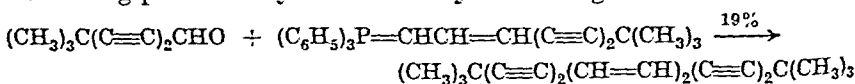
(80%) in the isomer mixture 83 is probably due to the presence of lithium bromide in the solution.



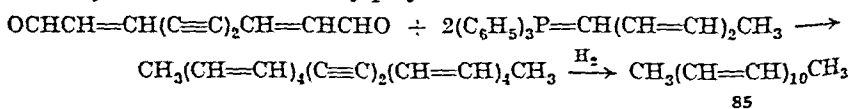
Both groups, R and R', may be unsaturated, as illustrated by the synthesis of hexa-3,5-dien-1-yne (84) from propargylaldehyde and allylidene triphenylphosphorane.¹⁷⁹



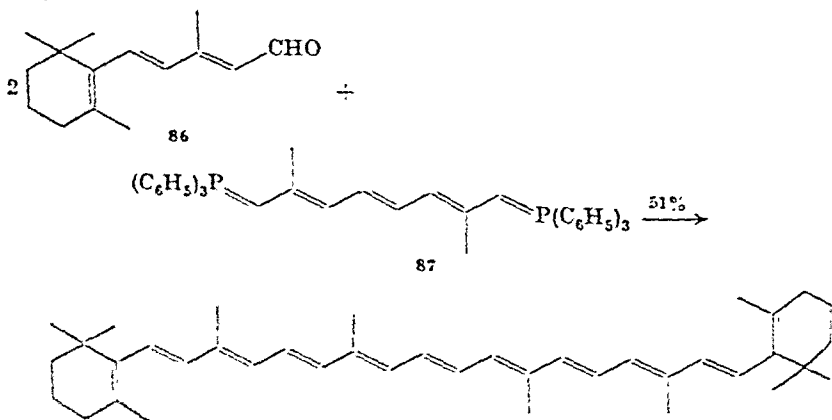
A series of compounds containing alternating double and triple bonds was synthesized in this way;¹⁸⁰ for instance, the C₂₀ hydrocarbon containing alternating pairs of ethylenic and acetylenic linkages.



The interaction of bifunctional carbonyl compounds with 2 equivalents of phosphorane can also be used for the preparation of polyenes, as shown in the synthesis of the dimethylpolyene 85.¹⁸¹



This method has proved especially valuable in the synthesis of carotenoids. Conversely, bifunctional phosphoranes can be used. Thus β -carotene (88) was prepared from β -ionylideneacetaldehyde (86) and the bis-ylide 87.⁸⁰

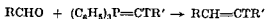


¹⁷⁹ Bollmann and Inhoffen, *Chem. Ber.*, **89**, 21 (1956).

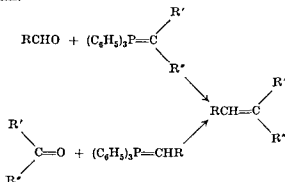
¹⁸⁰ Bollmann and Politt, *Chem. Ber.*, **90**, 130 (1957).

¹⁸¹ Bollmann and Mannhardt, *Chem. Ber.*, **89**, 1397 (1956).

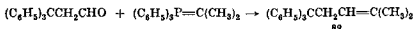
Tritium-labeled olefins have been prepared by the action of tritium-labeled alkylidene phosphoranes with aldehydes.⁶⁸



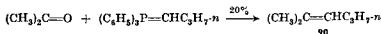
1,1,2-Trisubstituted ethylene derivatives may be prepared by two different paths.



By using the first path, 1,1,1-triphenyl-4-methyl-3-pentene (89) was obtained in 68% yield starting from β,β,β -triphenylpropionaldehyde.¹⁷⁸

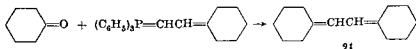


An illustration of the second method, which starts from ketones, is the preparation of a number of dimethylheptadienes (geraniolenes) and methylhexenes such as 2-methyl-2-hexene (90) from acetone and *n*-butyldenetriphenylphosphorane.¹⁸² This method has been applied most



frequently in the area of natural products chemistry. Bifunctional carbonyl compounds or bifunctional ylides (squalene synthesis) have been used for this purpose.

Starting from cyclic ketones, the corresponding exocyclic olefins are obtained, as shown by the preparation of dicyclohexylideneethane (91) from cyclohexanone.^{183,184}

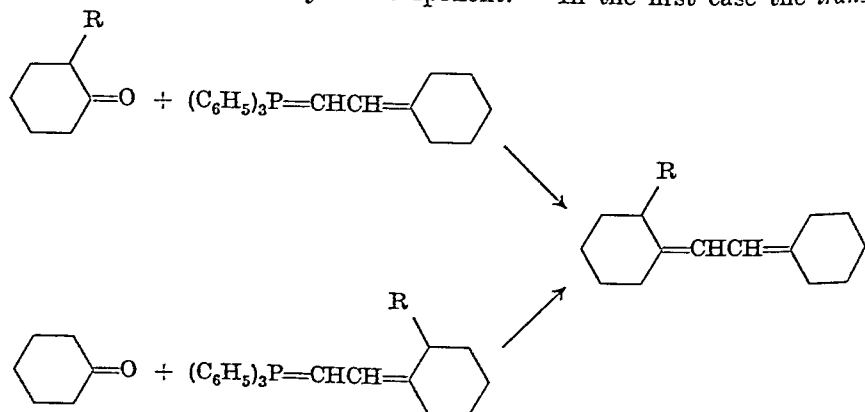


¹⁸² Ansell and Thomas, *J. Chem. Soc.*, 1961, 539.

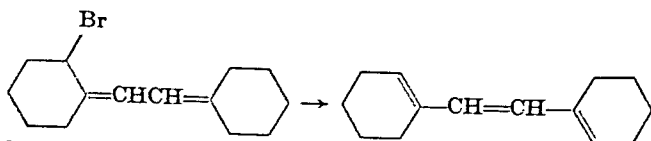
¹⁸³ Harrison, Lythgoe, and Trippett, *J. Chem. Soc.*, 1955, 4016.

¹⁸⁴ Harrison, Lythgoe, and Trippett, *Chem. Ind. (London)*, 1955, 507.

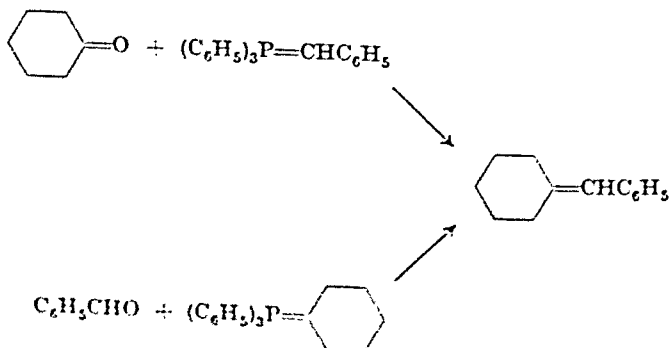
Substituted cyclohexanes have been prepared by variation of either the carbonyl^{158,183,184} or the ylide component.⁶⁹ In the first case the *trans*



compound, $\text{R} = \text{CH}_2\text{N}(\text{CH}_3)_2$, was obtained exclusively. In the second case, starting from the *cis* ylide, the *cis* compound, $\text{R} = \text{CH}_2\text{OH}$ or OH , was obtained predominantly; increasing the reaction temperature resulted in increased formation of the *trans* olefin. When the substituent R was Br , subsequent elimination of hydrogen bromide under the influence of the ylide was observed. The triene so obtained did not contain any exocyclic double bonds.¹⁶

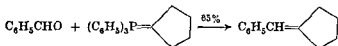


With benzylidenetriphenylphosphorane, cyclohexanone gives benzylidenecyclohexane in 60% yield.³ The same compound is obtained in 70% yield from the deep red cyclohexylidenetriphenylphosphorane and benzaldehyde.¹⁸⁵



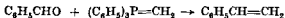
¹⁶ U. Scheelkopf, Doctoral Dissertation, Universität Tübingen, 1956.

Cyclopentylidenetriphenylphosphorane, another ylide containing an exocyclic double bond, is also intensely colored. It reacts with benzaldehyde to give benzylidenecyclopentane.¹⁸⁵

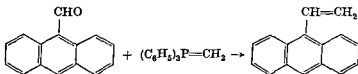


Aryl-Substituted Olefins

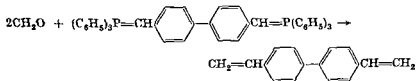
Styrene, the simplest monoaryl derivative of ethylene, has been obtained in 67% yield in the reaction of benzaldehyde with methylenetriphenylphosphorane.²



Similarly, 9-vinylnanthracene is obtained from 9-anthraldehyde.¹⁸⁶

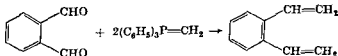


Vinyl aromatics are also accessible starting from the corresponding arylidene phosphoranes and formaldehyde,¹⁸⁷ as illustrated by the preparation of 4,4'-divinylbiphenyl in 80% yield. This route is especially



useful when the aromatic halogen compound is more accessible than the carbonyl compound. Aliphatic vinyl compounds may be prepared in a similar fashion.^{188,189}

From *o*-phthalaldehyde and methylenetriphenylphosphorane, *o*-divinylbenzene is formed in 75% yield.⁵²



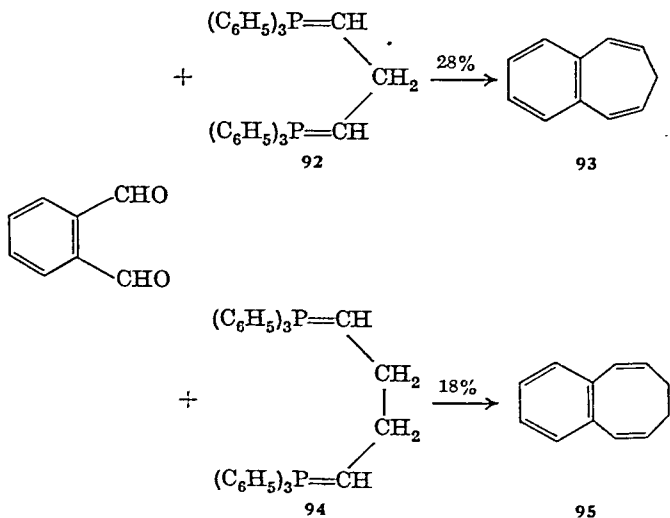
¹⁸⁵ Hawkins, *J. Chem. Soc.*, 1957, 3858.

¹⁸⁷ Drefahl, Plotner, and Rudolph, *Chem. Ber.*, **93**, 998 (1960).

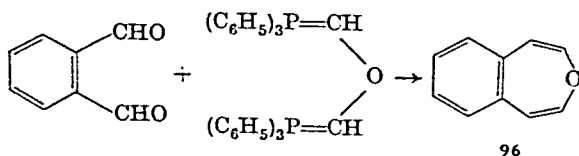
¹⁸⁸ Hauser, Miles, and Butler, 142nd Meeting, Am. Chem. Soc., Atlantic City, N J, Sept., 1962, Abstracts, p. 59Q.

¹⁸⁹ Hauser, Brooks, Miles, Raymond, and Butler, *J. Org. Chem.*, **28**, 372 (1963).

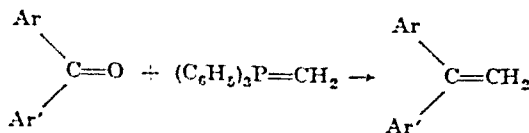
Starting from the bifunctional ylides **92** and **94**, 1,2-benzocyclohepta-1,3,6-triene (**93**) and 1,2-benzocycloocta-1,3,7-triene (**95**), respectively, are obtained.⁵²



3-Benzoxepin (**96**) was prepared in an analogous manner.¹⁹⁰



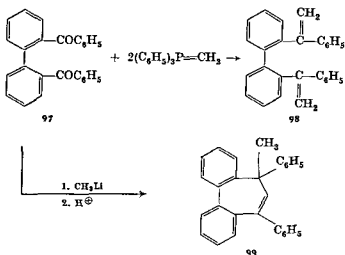
1,1-Diaryl olefins are particularly easy to obtain by the interaction of methylenetriphenylphosphorane and aromatic ketones.¹ Benzophenone



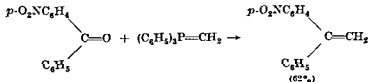
gave 1,1-diphenylethylene in 84% yield.¹ For preparative purposes, however, the Wittig reaction with aromatic ketones is of minor importance

¹⁹⁰ Bamforth and Pohl, *Angew. Chem.*, **73**, 426 (1961).

because aromatic ketones can usually be converted to the corresponding olefins without difficulty by the Grignard method, since an isomerization of the double bond cannot take place. There are reactions, however, in which the Grignard method fails to give the desired product. Thus the reaction of 2,2'-dibenzoylbiphenyl (97) with methyllithium followed by hydrolysis and dehydration gives the cyclic hydrocarbon 99 rather than 2,2'-distyrylbiphenyl (98), whereas the latter can be prepared in 85% yield by the Wittig reaction.¹⁹¹



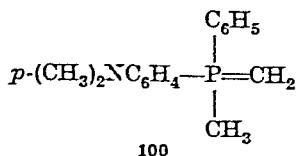
The preparation of olefins from nitro-substituted carbonyl compounds is not possible by the Grignard method because the reagent attacks nitro groups. This complication can usually be avoided by using an alkylidene phosphorane as in the accompanying example.²



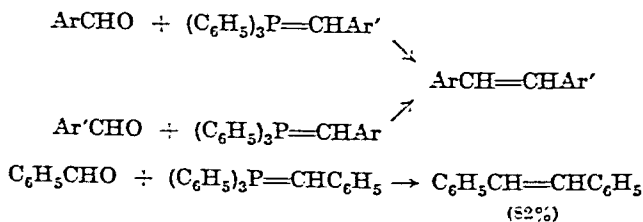
Only extremely nucleophilic alkylidene phosphoranes containing electron-releasing groups on phosphorus, such as 100, attack nitro groups. The ylide 100 has been reported to react with nitrobenzophenone to give

¹⁹¹ Wittig and Stolz, *Ann.*, 598, 93 (1956).

dark-colored products; olefin formation could not be observed.¹⁸² Normally, however, olefins are formed very readily from nitro ketones and nitro aldehydes, and yields of over 90% are not unusual.^{3,29,49,50,166,193}

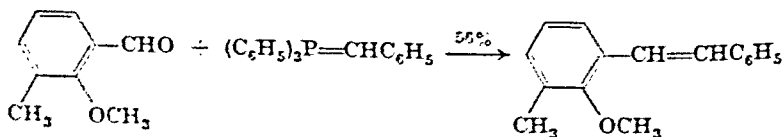


1,2-Diaryl olefins or stilbenes are formed in the interaction of aromatic aldehydes with aryl-substituted methylene triphenylphosphoranes. Mixtures of *cis* and *trans* olefins are obtained, the ratio in this synthesis of



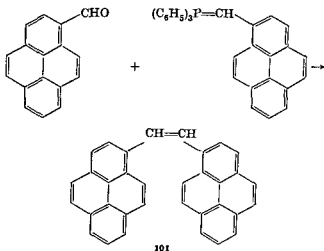
stilbene being 70% *trans* and 30% *cis*.² By using the alkoxide method, the ratio was found to be 47:53, the increased amount of the *cis* isomer being ascribed to increased polarity of the solvent.³ The different isomer ratios obtained in the synthesis of 4-nitro-4'-methoxystilbene by two different ways (Ar and Ar' exchanged) have been mentioned previously (p. 314).¹⁶⁸

Reaction of 2-methoxy-3-methylbenzaldehyde with benzyldene-triphenylphosphorane gives 2-methoxy-3-methylstilbene.¹⁹⁴ A large

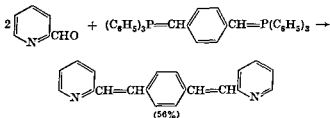


number of other stilbene derivatives has been prepared in a similar manner. The alkoxide method proved to be particularly useful for this

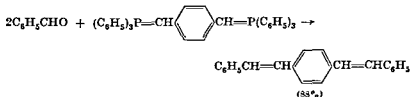
The preparation of symmetrical and unsymmetrical 1,2-diarylethylenes containing larger aromatic groups has also been reported.¹⁹⁷ 1,2-Bis-(3-pyrenyl)ethylene (101) is formed in 91% yield.



Stilbazole derivatives can be prepared from pyridine aldehydes.¹⁹⁸



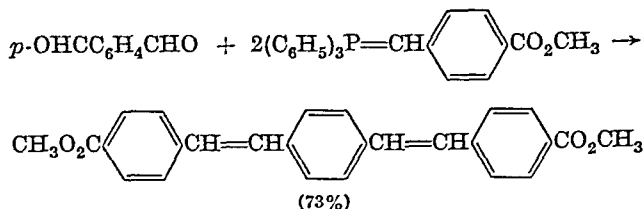
Distyrylbenzenes can be prepared similarly.^{66,193}



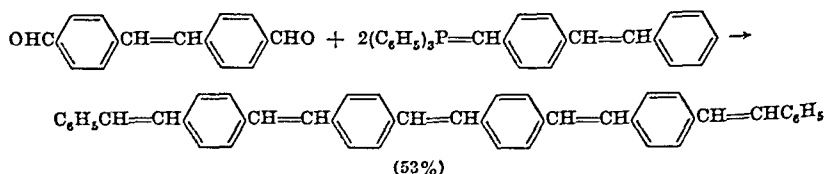
¹⁹⁷ Geerts and Martin, *Bull. Soc. Chim. Belges*, 69, 563 (1960) [*C.A.*, 55, 14410c (1961)].

¹⁹⁸ Drefahl, Plötner, and Buchner, *Chem. Ber.*, 94, 1824 (1961).

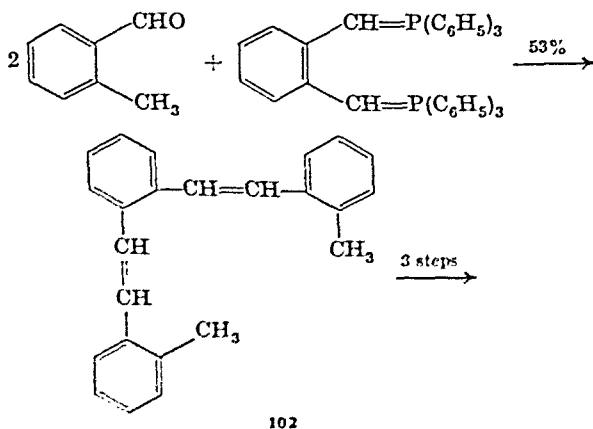
These compounds, which are of commercial interest as fluorescent brightening agents, can also be synthesized from terephthalaldehyde.^{66,193,199-201}



Longer chains with alternating benzene rings and ethylene groups can be prepared from stilbenedialdehyde.¹⁹⁶



1,3-Distyrylbenzenes⁶⁶ and 1,2-distyrylbenzenes^{201a} have also been synthesized. Starting from the 1,2-distyrylbenzene 102, the macrocyclic compound 103 can be prepared.^{201a}

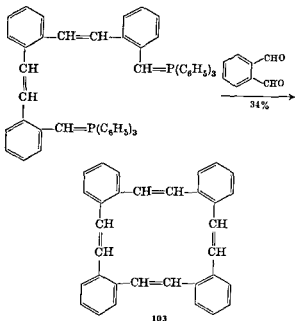


¹⁹³ Stilz, Pommer, Wolff, and Fessmann, Fr. pat. 1,266,688 (to BASF), 1959.

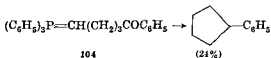
¹⁹⁹ Stilz, Pommer, Gehm, Schmidt, Mertens, Hehl, and Grunwald, Belg. pat. 599,794 (to BASF), 1959.

²⁰¹ Pommer, Siebel, Schwen, and Stilz, Belg. pat. 593,216 (to BASF), 1960.

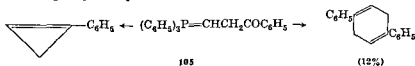
^{201a} Griffin, Martin, and Douglas, *J. Org. Chem.*, **27**, 1627 (1962).



Cyclic compounds may also be prepared by intramolecular Wittig reactions. Thus the alkylidene phosphorane **104**, which contains a carbonyl group, cyclizes to 1-phenylcyclopentene.²⁰²



2-Benzoyl-ethylidene-triphenylphosphorane (**105**), on the other hand, does not react intramolecularly to give 1-phenylcyclopropene. Instead an intermolecular condensation of two molecules of the phosphorane leads to 1,4-diphenyl-1,4-cyclohexadiene.²⁰³

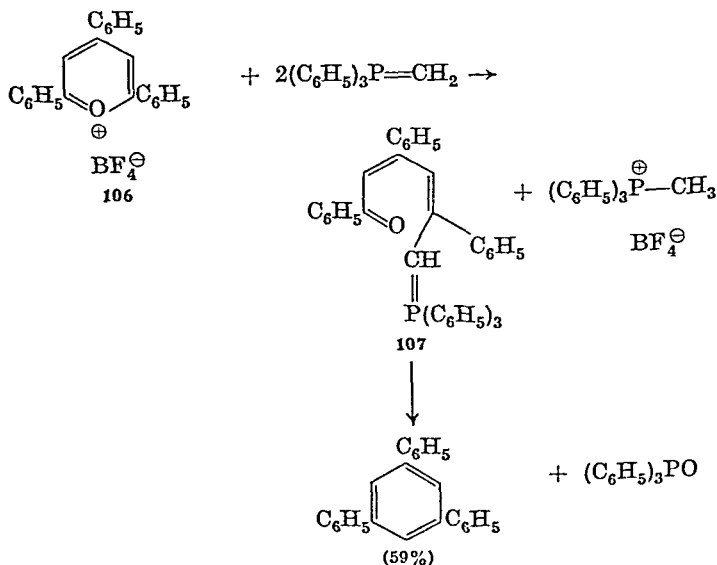


Aromatic compounds may also be prepared by using intramolecular Wittig reactions. The vinylog of benzoylmethylenetriphenylphosphorane

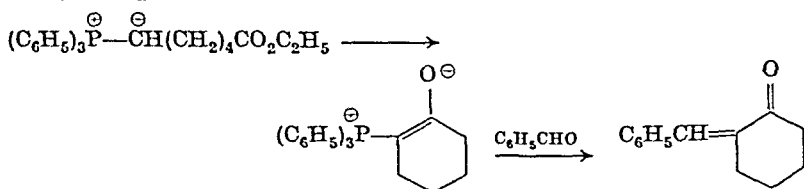
²⁰² Bieber and Eisman, *J. Org. Chem.*, **27**, 678 (1962).

²⁰³ Griffin and Witschard, *J. Org. Chem.*, **27**, 3334 (1962).

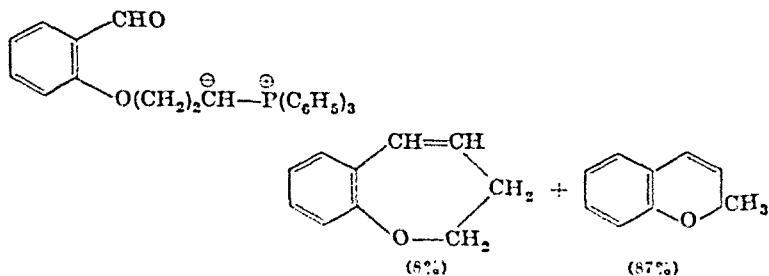
107, prepared from the pyrylium salt 106, cyclizes to symmetrical triphenylbenzene.²⁰⁴



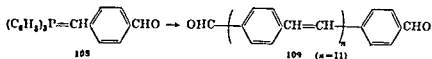
Cyclizations may also occur in the ylide prior to condensation with a carbonyl component.²⁰⁵



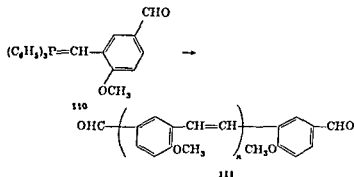
A cyclization has also been reported in which a rearrangement occurred in the alkylidene group of the phosphorane.²⁰⁶



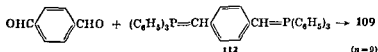
If there is no possibility for intramolecular ring closure, an intermolecular reaction may take place exclusively. *p*-Formylbenzylidenetriphenylphosphorane (108), for instance, polymerizes spontaneously to give a lemon-yellow compound 109 which melts above 360°.²⁰⁷



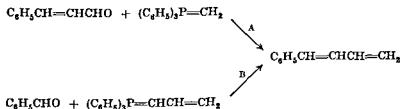
In a similar fashion, the colorless poly-*m*-xylylidene derivative **111**, m.p. 180° is obtained from the ylide **110**.²⁰⁸



Polymerizations also can be effected by interaction of bifunctional carbonyl compounds with bis-ylides. Terephthalaldehyde reacts quantitatively with the bifunctional phosphorane **112** to give a yellow poly-*p*-pylylidene which, except for its degree of polymerization, is probably identical with the product **109** mentioned above.²⁰⁸



By means of the Wittig reaction, a large number of aryl-substituted butadiene derivatives and polyenes has been prepared. 1-Phenylbutadiene was obtained in two different ways.² Starting from cinnamaldehyde

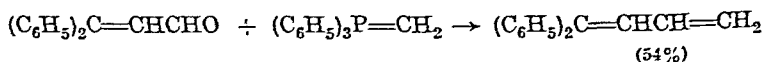


¹⁰⁷ A. Haag, Doctoral Dissertation, Universität Heidelberg, 1962.

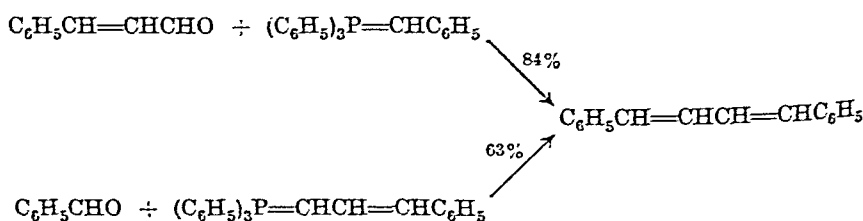
⁸⁰⁸ McDonald and Campbell, *J. Am. Chem. Soc.*, **82**, 4669 (1960).

(path A), no isomerization of the double bond took place and the *trans* isomer was obtained exclusively in 69% yield. Path B, on the other hand, gave 58% of a mixture containing 55% *trans*- and 45% *cis*-phenylbutadiene.

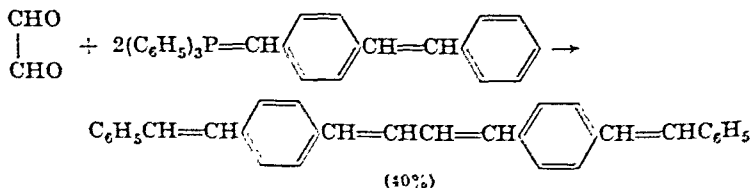
1,1-Diphenylbutadiene was prepared from β -phenylcinnamaldehyde by using path A.¹²³



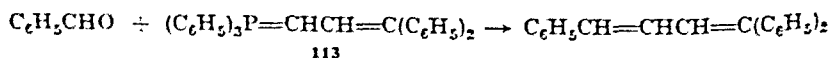
1,4-Diarylbutadiene derivatives may also be obtained by two different methods.^{65,209-211}



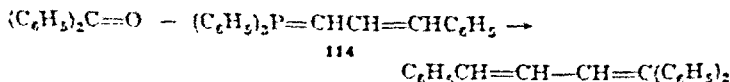
Paths A and B have been used for the synthesis of a large number of unsymmetrically substituted 1,4-diarylbutadienes.^{210,211} The symmetrically substituted compounds may also be prepared by a third method in which glyoxal is the starting carbonyl compound.²¹¹



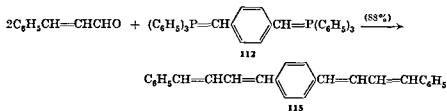
A number of 1,1,4-triarylbutadienes was prepared from the alkylidene phosphorane 113.²¹¹ For example,



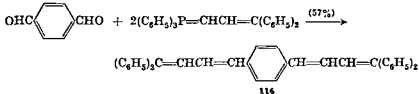
The same diene is formed in 64% yield by the action of cinnamylidene-triphenylphosphorane (114) on benzophenone.¹²⁵



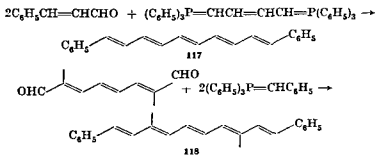
p-Bis-(4-arylbutadienyl)benzenes have been prepared by starting from bifunctional ylides^{66,210} and from bifunctional carbonyl compounds.^{66,211} The synthesis of *p*-bis-4-phenylbutadienylbenzene (115) is an example of the first route,²¹⁰ and the synthesis of *p*-bis(4,4-diphenylbutadienyl)-



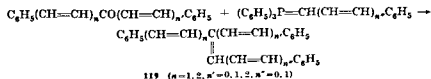
benzene (116) is an example of the second.²¹¹



The synthesis of higher diarylpolyenes is effected in basically the same way, starting either from bifunctional ylides or from dicarbonyl compounds as illustrated by the synthesis of 1,10-diphenyldecapentaene (117)^{209,212} and its dimethyl derivative 118²⁰⁹ by two different methods.



Finally, the preparation of the cross-conjugated chromophore systems 119 has been reported.²¹³

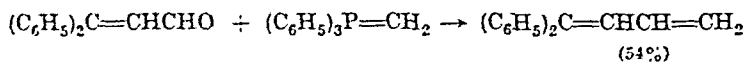


²¹² Heitman, Sperna Weiland, and Huismann, *Koninkl. Ned. Akad. Wetenschap., Proc., Ser. B.*, **64**, 165 (1961) [*C.A.*, **55**, 17562f (1961)].

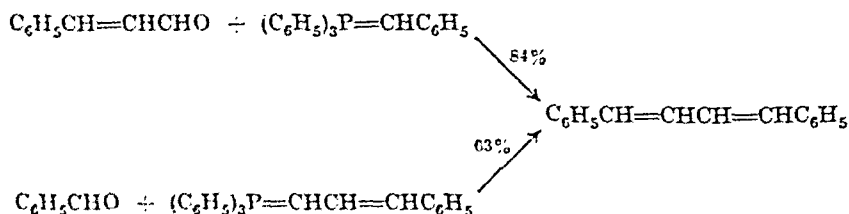
²¹³ Bohlmann, *Chem. Ber.*, **89**, 2191 (1956)

(path A), no isomerization of the double bond took place and the *trans* isomer was obtained exclusively in 69% yield. Path B, on the other hand, gave 58% of a mixture containing 55% *trans*- and 45% *cis*-phenylbutadiene.

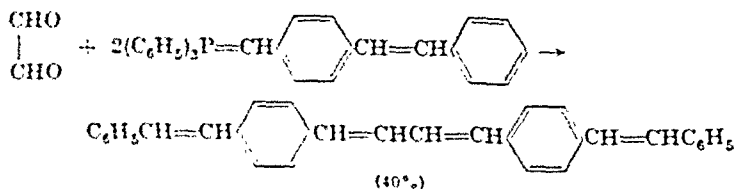
1,1-Diphenylbutadiene was prepared from β -phenylcinnamaldehyde by using path A.¹²⁸



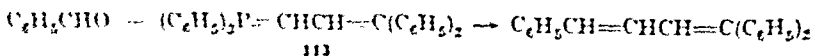
1,4-Diarylbutadiene derivatives may also be obtained by two different methods.^{63,209-211}



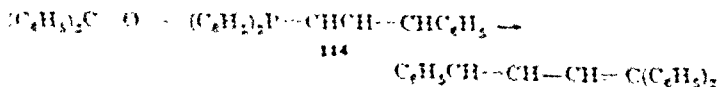
Paths A and B have been used for the synthesis of a large number of unsymmetrically substituted 1,4-diarylbutadienes.^{210,211} The symmetrically substituted compounds may also be prepared by a third method in which glyoxal is the starting carbonyl compound.²¹¹



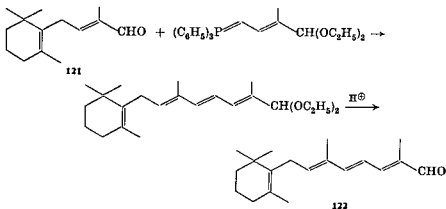
A number of 1,1,4-triarylbutadienes was prepared from the alkylidene phosphorane 113.²¹¹ For example,



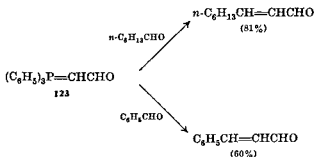
The same diene is formed in 64% yield by the action of cinnamylidene-triphenylphosphorane (114) on benzophenone.¹²⁹



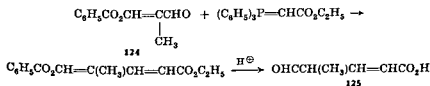
Alternatively, a monocarbonyl compound may be made to react with an alkylidene phosphorane containing an acetal group which is subsequently converted to the aldehyde by treatment with acid.²¹⁶ Thus the β -C₁₄ aldehyde **121** was converted in 78% yield to the β -C₁₉ aldehyde **122**.



The carbonyl group in resonance-stabilized formylalkylidenetriphenylphosphoranes, for example, **123**, need not be protected. Reaction with aldehydes gives α,β -unsaturated aldehydes in good yields.^{33,58,116}



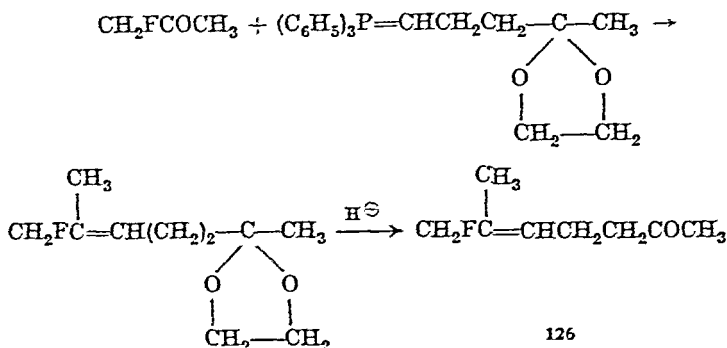
The β,γ -unsaturated aldehyde **125** has been prepared from the enol ester **124**, the ester group being subsequently removed by saponification.²¹⁷



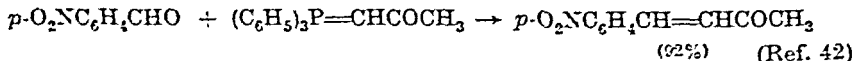
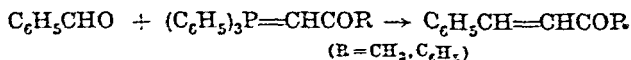
²¹⁶ Makin, *Dokl. Akad. Nauk SSSR*, **133**, 387 (1961) [*C.A.*, **55**, 20989 (1961)].

²¹⁷ Kucherov, Yanovskaya, and Kovalev, *Dokl. Akad. Nauk SSSR*, **133**, 370 (1960) [*C.A.*, **54**, 24699h (1960)].

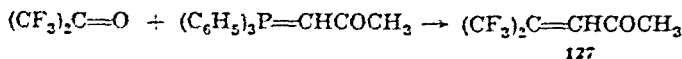
Ketones. Unless there is the possibility of a resonance interaction with the ylene double bond, keto groups in alkylidene phosphoranes must be protected, preferably by conversion to a ketal, as illustrated by the synthesis of 7-fluoro-6-methylhept-5-en-2-one (126).²¹⁸



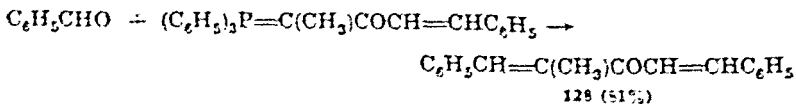
Acylmethylene phosphoranes, on the other hand, are stable and may be used directly in the synthesis of α,β -unsaturated ketones.³¹



Reactions of ketones with acylmethylene triphenylphosphoranes, as with all other resonance-stabilized ylides, take place less readily.³¹ An exception is the formation of the unsaturated fluoroketone 127 in 93% yield.²¹⁹

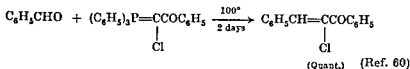


α,β -Unsaturated ketones substituted on the α -position are accessible in a similar way, as illustrated by the preparation of the ketone 128.²²

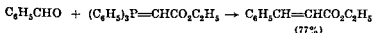


α -Halo- α,β -unsaturated ketones have also been prepared by this method; forcing conditions are required.^{23,60} The highest yields were obtained by using excess aldehyde as the solvent. No reaction was

observed when α -haloacylmethylene triphenylphosphoranes were heated with ketones in benzene for several hours.⁵⁹



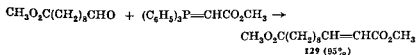
Carboxylic Esters and Other Acid Derivatives. The interaction of carbalkoxymethylene triphenylphosphoranes with carbonyl compounds leads to α,β -unsaturated carboxylic esters. Aldehydes react very readily, as illustrated by the preparation of ethyl cinnamate.³ Analogously,



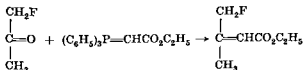
good yields of nitrocinnamic esters were obtained from *o*-, *m*-, and *p*-nitrobenzaldehyde.¹⁶²

The successful reaction of carbethoxymethylenetriphenylphosphorane with heterocyclic aldehydes such as furfural,²²⁰ pyridine aldehydes,³⁴ and 8-xanthinecarboxaldehyde²²¹ has also been reported.

Aliphatic aldehydes are also easily converted to α,β -unsaturated carboxylic esters, as illustrated by the preparation of 1,9-bis(methoxycarbonyl)decene (129).¹⁶¹



Reactions of ketones with carbalkoxymethylene triphenylphosphoranes occur, as a rule, much less readily. The ease of reaction of fluoroacetone is an exception.²¹⁸

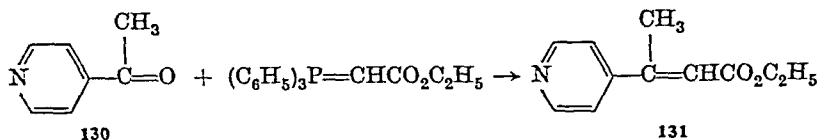


Aromatic or aliphatic ketones, however, will give satisfactory yields in their reactions with carbalkoxymethylene triphenylphosphoranes only

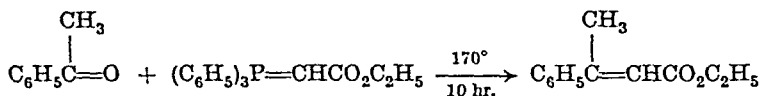
²²⁰ Kucherov, Kovalev, Nazarova, and Yanovskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1960, 1512 [*C.A.*, 55, 1420b (1961)].

²²¹ Brederick and Föhlsch, *Chem. Ber.*, 95, 414 (1962).

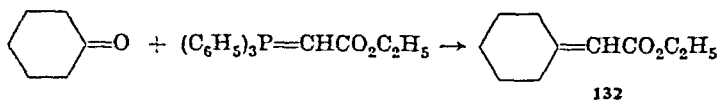
after reaction times of several days at room temperature³⁴ or several hours at 100–170°.³⁵ Thus the ketone 130 reacts slowly in ethanol at 20° with carbethoxymethylenetriphenylphosphorane to give the ester 131 in 90% yield after several days.³⁴



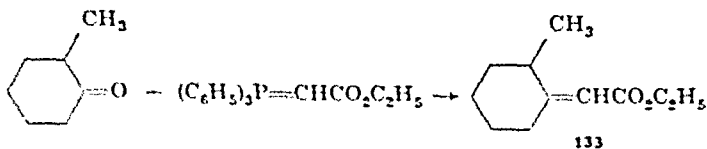
Heating the same ylide with acetophenone without a solvent gives ethyl β -methylcinnamate in 58% yield.³⁵



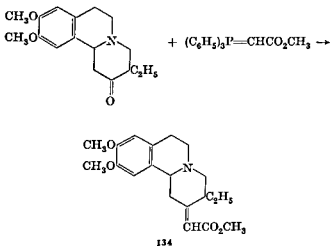
The preparation of esters containing exocyclic double bonds from cyclic ketones also requires forcing conditions.^{34,35} Ethyl cyclohexylideneacetate (132) is formed in 44% yield in ethanol solution at room temperature within 1 week;³⁴ heating the reactants without solvent to 170° for 10 hours gives a yield of 60%.³⁵



Substituents in the α -position to the carbonyl group further reduce the reactivity of ketones. Thus 61% of the ketone was recovered when a mixture of 2-methylcyclohexanone and carbethoxymethylenetriphenylphosphorane was kept at room temperature for 12 days; the yield of ethyl 2-methylcyclohexylideneacetate (133) was only 7%.³⁴



In general, it is advantageous to use high temperatures and little or no solvent when sterically hindered ketones are employed.³⁶ Thus, in the reaction of 2-methylcyclohexanone mentioned above, the yield of the ester 133 was increased to 30% by heating the reactants without solvent to 150°.³⁶ Under the same conditions, the tricyclic compound 134 could be obtained in 58% yield.³⁶



134

Reactions like these take place much more readily in the presence of benzoic acid as a catalyst.³⁹

Substitution of phenyl groups on phosphorus by electron-releasing groups also results, under otherwise equal conditions, in an increase of the yields.^{28,53,222-226}

In the reactions of dicarbonyl compounds with 1 mole of carbomethoxymethylenetriphenylphosphorane, it is usually possible to isolate the compound resulting from conversion of only one carbonyl group to an olefin.²²⁷⁻²²⁹ Thus the monoketone 136 is obtained in 93% yield by the

³⁹ Trippett and Walker, *Chem. Ind. (London)*, 1960, 933.

⁵³ Horner, Hoffmann, and Wippel, *Chem. Ber.*, **91**, 61 (1958).

²²² Horner, Hoffmann, Wippel, and Klahre, *Chem. Ber.*, **92**, 2499 (1959).

²²³ Horner, Hoffmann, Klink, Ertel, and Toscano, *Chem. Ber.*, **95**, 581 (1962).

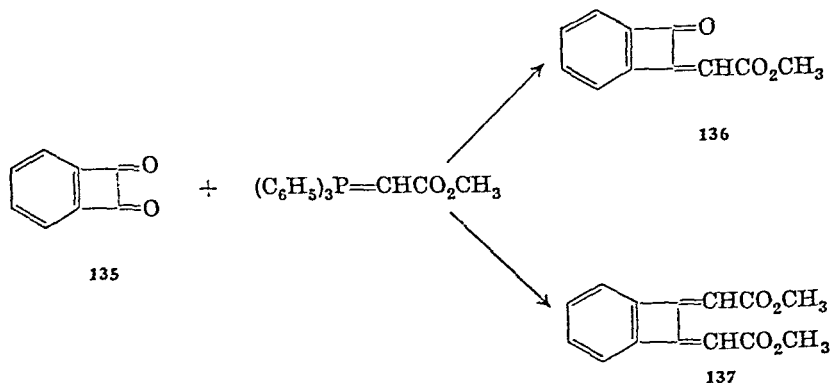
²²⁴ Wadsworth, Jr., and Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

²²⁷ Cava and Pohl, *J. Am. Chem. Soc.*, **82**, 5242 (1960).

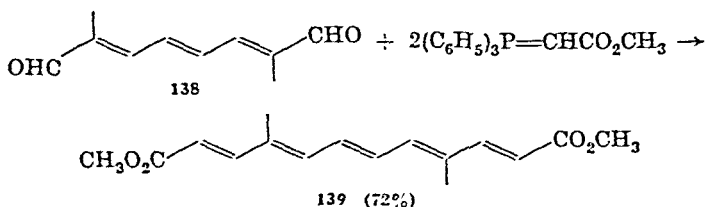
²²⁸ Eiter, *Angew. Chem.*, **73**, 619 (1961).

²²⁹ Eiter, *Ann.*, **658**, 91 (1962).

interaction of benzocyclobutenedione (135) with 1 mole of ylide, whereas with 2 moles of ylide the final product 137 is formed in 85% yield.²²⁷



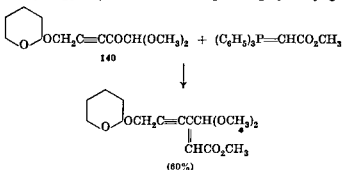
Unsaturated dialdehydes such as 138 lead to polyene dicarboxylic esters, as illustrated by the synthesis of the ester 139.²³⁰ Methylbixin,



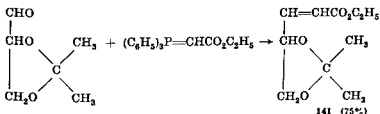
crocin dimethyl ester^{39,231-235} and a large number of other polyene dicarboxylic esters^{163,236} have been prepared in this way.

In compounds containing both a keto and an aldehyde group, the latter reacts preferentially. If conversion of the keto group to an olefin is to be effected, the aldehyde group must be protected by acetal formation, as illustrated by the reaction of the carbonyl compound 140 with carbo-methoxymethylenetriphenylphosphorane.²³⁷

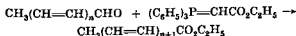
In the ketone 140, a hydroxyl group has also been protected by conversion to its tetrahydropyranyl ether. Two neighboring hydroxyl groups, as in



sugars, may also be blocked by ketal formation, as shown by the interaction of the dimethylketal of D-glyceraldehyde with carbethoxymethylenetriphenylphosphorane to form the ester 141.²³⁸

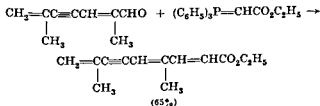


Polyene aldehydes react with carbalkoxymethylene triphenylphosphoranes to form polyene carboxylic esters which contain one more double bond than the aldehyde. For $n = 1$ through 4, the yields are



higher than 80%.²²⁰

Polyene aldehydes containing triple bonds may also be employed in this reaction,²³⁹ which has been used extensively for the synthesis of

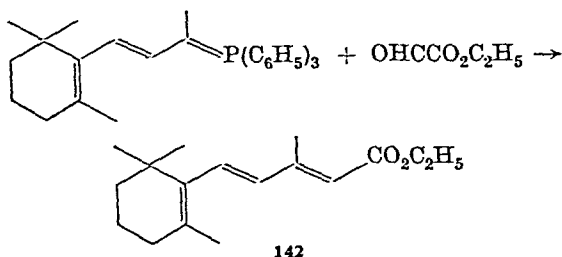


carboxylic esters in the carotene series.

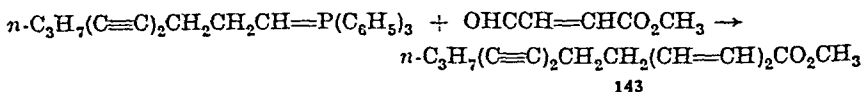
²¹⁸ Kuhn and Brossmer, *Angew. Chem.*, **74**, 252 (1962).

²³⁹ Yanovskaya, Kucherov, and Kovalev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1962**, 674 [*C.A.*, **57**, 16379a (1962)].

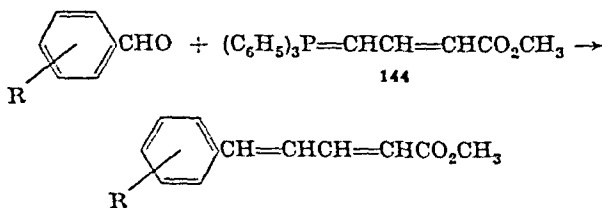
α,β -Unsaturated carboxylic esters may also be obtained from a glyoxylic ester or its vinylogs, as illustrated by the preparation of ethyl β -ionylideneacetate (142).²⁴⁰



In order to prevent side reactions involving the ester group, it has been proposed to add the ylide solutions to the aldehyde and not vice versa. This procedure furnished the unsaturated ester 143 in 46% yield.²⁴¹



Instead of a vinylog of glyoxylic ester, a vinylog of a carbalkoxy-methylenephosphorane may also be used as illustrated by the reaction of substituted benzaldehydes with the phosphorane 144.²⁴² The phosphorane 144 is easily accessible from methyl γ -bromocrotonate. A



comparison of the results obtained by this reaction with those obtained in the Reformatsky reaction showed that the Wittig reaction is definitely to be preferred, especially with benzaldehydes containing nitro, dimethyl-amino, or chloro substituents. Even when comparable yields are obtained by both methods, the Wittig reaction has the advantages of convenience and speed. By using ultraviolet spectroscopy it was shown that the reaction was practically complete after 5 minutes. The only exception occurs in reactions using 2,4,6-trimethoxybenzaldehyde for which the

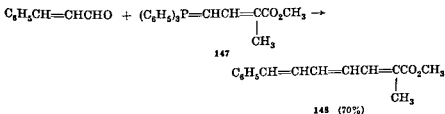
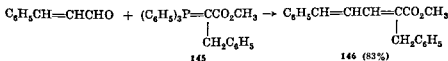
²⁴⁰ Pomett and Sarnacki, *Ger. pat.* 1,068,706 (to BASF) [*C.A.*, **56**, 512a (1962)].

²⁴¹ Bollmann and Inhoffen, *Chem. Ber.*, **89**, 1276 (1956).

²⁴² Bollmann, *Chem. Ber.*, **90**, 1519 (1957).

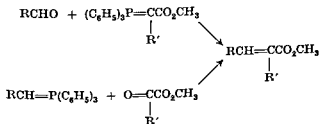
Reformatsky reaction is superior. It is of interest to note that aldehydes containing *o*-hydroxyl groups can also be employed in the Wittig reaction.

The reaction between aldehydes and carbalkoxy ylides containing α -alkyl substituents leads to α -branched α,β -unsaturated carboxylic esters. Thus cinnamaldehyde and the phosphorane 145 give the α -substituted ester 146.^{40,111} The vinylogous ylide 147 furnishes the corresponding hexatrienecarboxylic ester 148.^{232,235} By employing this

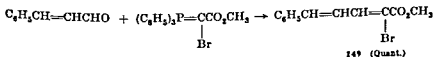


method and starting from polyene dialdehydes, branched polyene dicarboxylic esters have been prepared.³⁹

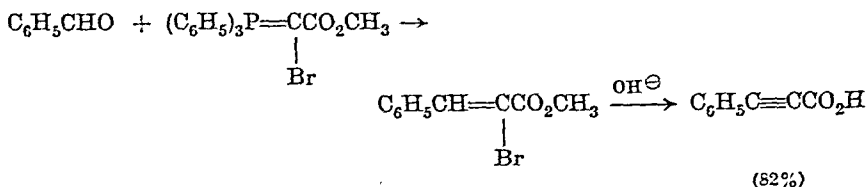
Whereas in all these reactions using resonance-stabilized phosphoranes the *trans* olefin is formed predominantly, interaction of reactive ylides with α -keto esters leading to α,β -unsaturated esters always yields a considerable amount of the *cis* isomers.¹⁶⁴



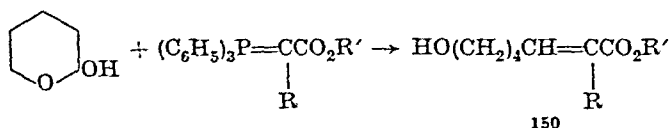
Similarly, α -halo- α,β -unsaturated carboxylic esters^{60,117} are prepared from halocarbomethoxymethylene triphenylphosphoranes and aldehydes, as illustrated by the synthesis of the ester 149.¹¹⁷



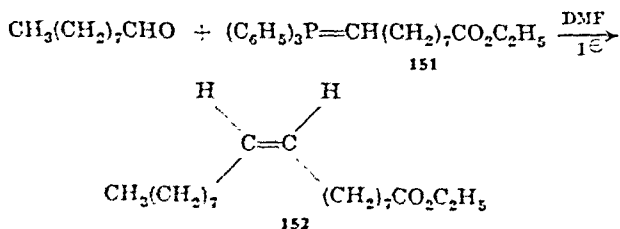
α -Halo- α,β -unsaturated carboxylic esters that easily eliminate hydrogen halide furnish substituted propiolic acids on saponification.¹¹⁷



Esters of ω -hydroxy- α,β -unsaturated carboxylic acids (150) are formed by the interaction of 2-hydroxytetrahydropyran with carbalkoxy-alkylidene triphenylphosphoranes.¹¹⁴ The *trans* isomer is formed almost exclusively.

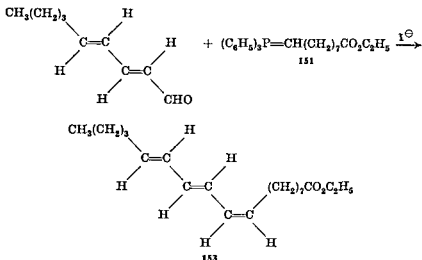


cis-Carboxylic esters are obtained only if there is no possibility for resonance interaction between the ester group and the ylene double bond. By using dimethylformamide as the solvent and preferably in the presence of iodide ion, the *cis* compounds are formed almost exclusively.^{114,170,171} Pelargonaldehyde and the ylide 151, for instance, give ethyl oleate (152) stereospecifically in 73% yield.^{114,170} Probably as a

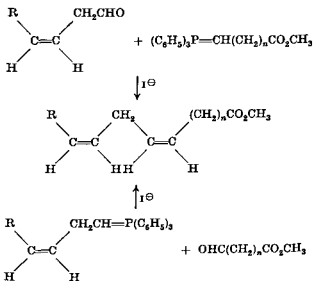


consequence of the solvation of this ylide in the polar solvent, the ester group in the reactive phosphorane 151 remains essentially unattacked. In other circumstances an ester group remote from the ylide portion of the molecule may, however, be attacked.²⁰⁵

Ethyl α -eleostearate (153) was also synthesized from the ylide 151.¹¹⁴

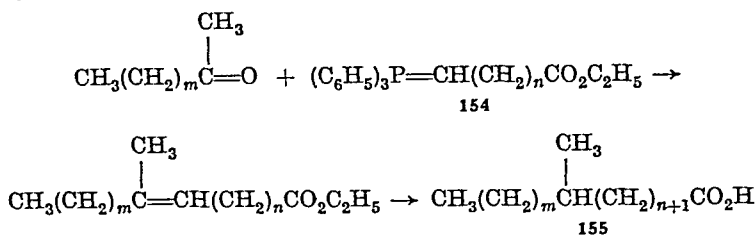


Again, this type of compound may be prepared by two different ways, as illustrated by the synthesis of the biologically important acids of the *cis-cis*-divinylmethane type.¹¹⁴

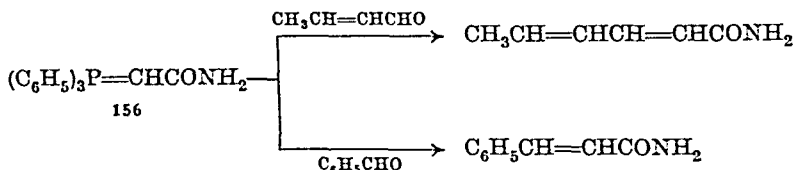


The reaction between ketones and alkylidene phosphoranes of the type 154 is not stereospecific, but saturated branched fatty acids such as

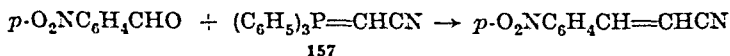
155 can be obtained in good yield by saponification followed by catalytic hydrogenation.¹¹⁴



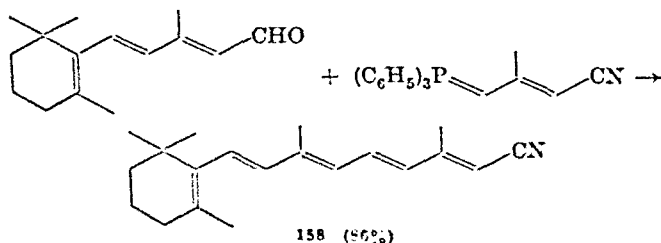
Unsaturated amides and nitriles have also been synthesized. Thus carbamidomethylenetriphenylphosphorane (156) reacts with crotonaldehyde to give the amide of sorbic acid,²⁴³ and with benzaldehyde to give cinnamamide.⁵⁸



The interaction of cyanomethylenetriphenylphosphorane (157) with benzaldehyde and its derivatives gives the corresponding cinnamonitriles in good yields.^{42,43,58} *p*-Nitrocinnamonitrile, for instance, is obtained from *p*-nitrobenzaldehyde in 74% yield.⁴²



As illustrated by the synthesis of the vitamin A₂ carbonitrile (158), vinylogous cyanomethylene triphenylphosphoranes can also be employed as starting materials.²⁴⁴

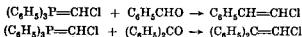


¹¹⁴ Wittig and Pommer, Ger. pat. 943,648 (to BASF) [C.A., 52, 16292d (1958)].

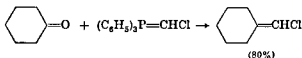
²⁴⁴ Ester, Oediger, and Trusheit, Ger. pat. 1,110,633 (to Farb. Bayer) [C.A., 56, 3522c (1962)].

Vinyl Halides

Monohaloolefins are formed in the reaction of halomethylene triphenylphosphoranes with aldehydes and ketones.^{91,92} Benzaldehyde and benzophenone react with chloromethylenetriphenylphosphorane to give the corresponding vinyl halides in 67% yield.⁹²

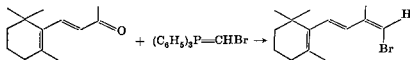


Aliphatic ketones can also be converted to vinyl chlorides.^{95,96} If the

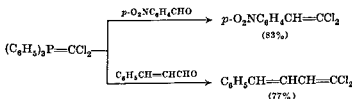


ylides are generated from triphenylphosphine and carbenes, the yields on the average decrease to 30%.⁹⁶

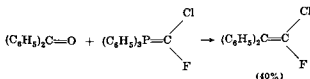
The preparation of vinyl bromides has also been reported. The reaction with β -ionone, for instance, proceeds in 70% yield.⁹⁴



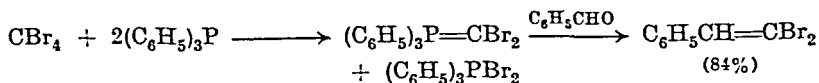
1,1-Dihaloolefins are obtained from dihalomethylene triphenylphosphoranes.^{92,93,94,98} The reactions with dichloromethylenetriphenylphosphorane are illustrative.



The preparation of mixed haloolefins is exemplified by the reaction of fluorochloromethylenetriphenylphosphorane with benzophenone⁹⁴

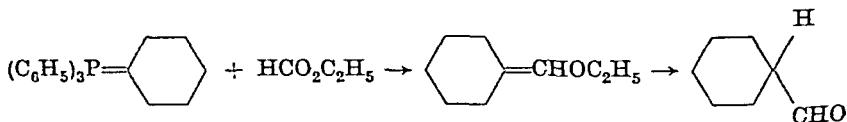


Since carbon tetrachloride⁹⁸ and carbon tetrabromide⁸² react directly with triphenylphosphine with the formation of dihalomethylene triphenylphosphoranes, 1,1-dihaloölefins can be prepared in one step by carrying out this reaction in the presence of carbonyl compounds.



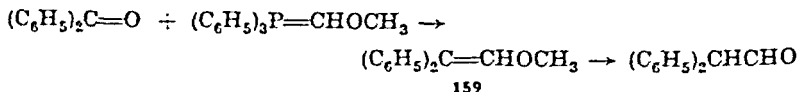
Vinyl Ethers

The synthesis of vinyl ethers is important because they can be converted to aldehydes by saponification. The original procedure consisted of slow addition of formic ester to the alkylidene phosphorane followed by acid hydrolysis of the initially formed enol ether.¹¹³ Hexahydrobenzaldehyde was obtained in moderate yield in this way, which is a general method for

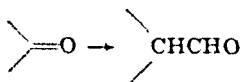


the conversion of a halogen compound to an aldehyde containing one more carbon atom. Since, however, the formic ester is partially cleaved by the ylide into carbon monoxide and alcohol, the yields are usually not very good.²⁴⁵

A better synthesis of vinyl ethers involves the reaction of a carbonyl compound with an alkoxymethylene triphenylphosphorane.^{92, 246-248} For example, benzophenone reacts with methoxymethylenetriphenylphosphorane to give 1,1-diphenylvinyl methyl ether (159) in 83% yield;²⁴⁷ treatment with acid gives diphenylacetaldehyde.

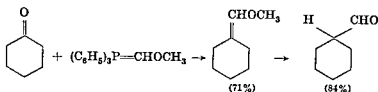


The over-all result is the conversion of a carbonyl compound to an aldehyde containing one more carbon atom. The best reagent for the

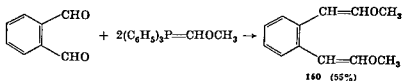


occasionally difficult hydrolysis of the enol ether is perchloric acid in diethyl ether.²⁴⁸

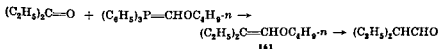
Cyclic ketones may also be subjected to this reaction. Cyclohexanone is converted to methoxymethylenecyclohexane which yields hexahydrobenzaldehyde on heating with ethereal perchloric acid.²⁴⁸



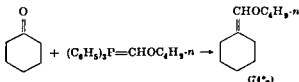
Alkoxymethylene triphenylphosphoranes are relatively unstable at room temperature. It is therefore advantageous to prepare them at as low a temperature as practicable and to add the carbonyl compound before warming the reaction mixture to room temperature.⁸⁷ The alkoxide method is of advantage with carbonyl compounds that are stable to alkoxides, as in the synthesis of 160.⁸²



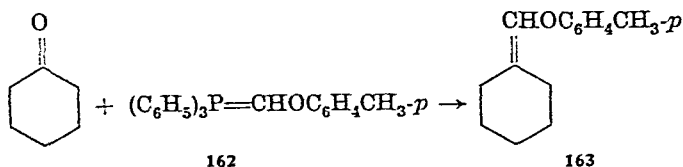
n-Butoxymethylenetriphenylphosphorane is less stable than methoxymethylenetriphenylphosphorane.⁸⁷ Low temperatures are therefore particularly important in the synthesis of butyl vinyl ethers. When diethyl ketone was allowed to react with *n*-butoxymethylenetriphenylphosphorane at -40° and the reaction mixture was then left at room temperature for several hours, 1-*n*-butoxy-2-ethylbutene (161) was obtained in 73% yield.²⁴⁸



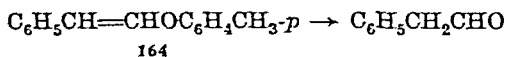
Hydrolysis of the ether with perchloric acid furnished diethylacetaldehyde in 70% yield. Cyclic ketones react analogously.²⁴⁸



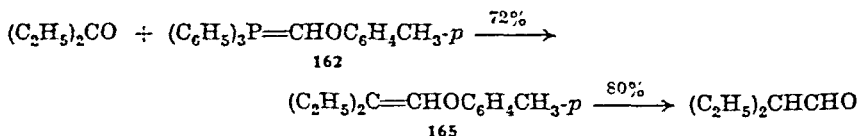
Aryloxymethylene triphenylphosphoranes are more stable than alkoxymethylene triphenylphosphoranes. Vinyl aryl ethers are therefore particularly accessible. For example, *p*-methylphenoxy-methylenecyclohexane (163) is obtained in 82% yield by allowing *p*-methylphenoxy-methylenetriphenylphosphorane (162) to interact with cyclohexanone in ether at room temperature for 2 hours.²⁴⁸



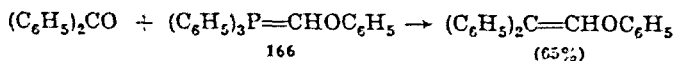
β -(*p*-Methylphenoxy)styrene (164), obtained similarly in 75% yield from benzaldehyde, could be readily hydrolyzed with perchloric acid²⁴⁶ to give phenylacetaldehyde in 73% yield.²⁴⁸



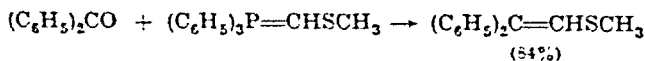
In the same way, diethylacetaldehyde is prepared from diethyl ketone by way of diethylvinyl *p*-tolyl ether (165).²⁴⁸



Vinyl phenyl ethers may be obtained from phenoxy-methylenetriphenylphosphorane (166).²⁴⁹



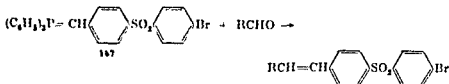
Vinyl thio ethers have also been prepared by this method.⁹² They are hydrolyzed to aldehydes much less readily.



Analytical Applications

The alkylidene phosphorane 167 has been suggested as a specific reagent for the characterization of aldehydes in the presence of ketones.²⁴⁷⁻²⁵¹ In ethanol-water (95:5) at 75° it reacts readily with all aldehydes

investigated but not with ketones. The reactions are complete when the yellow color of the ylide disappears. In pure ethanol, ketones react to a

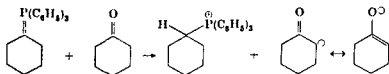


limited extent (5–10%); on addition of 5% water, only aldehydes react and the yields are between 50% and 90%. The Wittig reagent 167 may therefore be used for the selective characterization and identification of aldehydes.

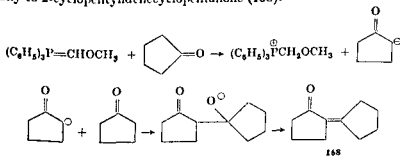
Side Reactions

Fortunately, side reactions occur only rarely and can usually be suppressed by suitable choice of conditions. The handling of unstable alkylidene phosphoranes has already been mentioned. Reactions are either carried out at low temperatures, or the alkoxide method which permits interaction of the carbonyl compound with the alkylidene phosphorane *in statu nascendi* is used.

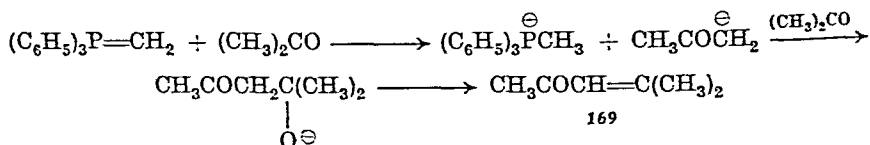
The strongly basic alkylidene phosphoranes can also function as proton acceptors to remove a proton from the α -position of carbonyl compounds. This reaction is particularly pronounced with easily enolizable ketones such as cyclohexanone and cyclopentanone. If the reaction between the ylide and the carbonyl compound is sterically hindered, enolization becomes the main reaction¹⁸⁵



Methoxymethylenetriphenylphosphorane converts cyclopentanone partially to 2-cyclopentylidenecyclopentanone (168).²⁴⁸

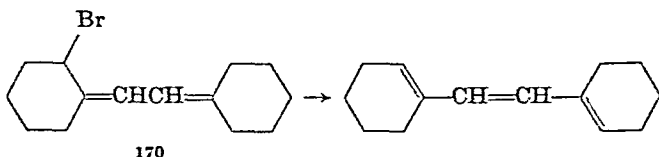


Analogous condensations have been observed to a lesser extent with acetone, which is partially converted to mesityl oxide (169) by Wittig reagents.¹⁸² Because decreasing temperatures favor the Wittig reaction

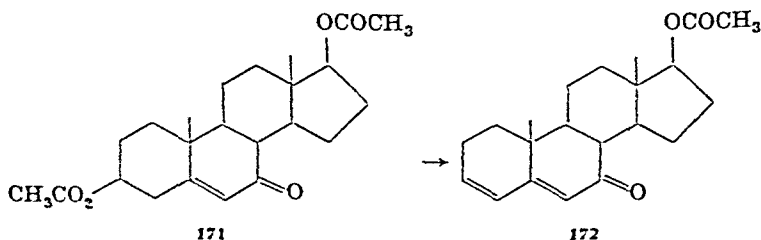


over aldol condensations, reactions with enolizable ketones are best done at low temperatures.²⁴⁸

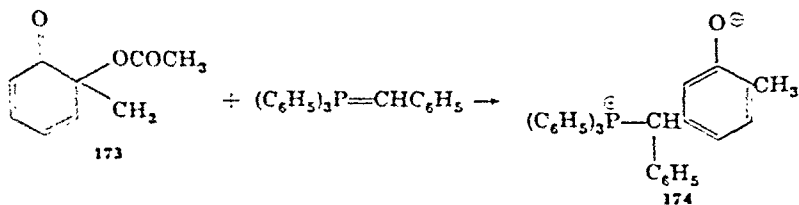
The elimination of acids from reactants or products under the influence of Wittig reagents has also been observed. An example is the elimination of hydrogen bromide from the diene 170.¹⁶



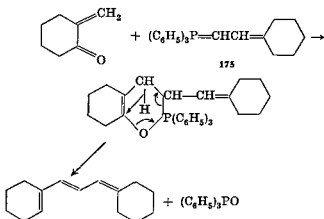
In the reaction of methylenetriphenylphosphorane with the keto steroid 171, the expected product is accompanied by the dienone 172 formed by elimination of acetic acid.²⁵²



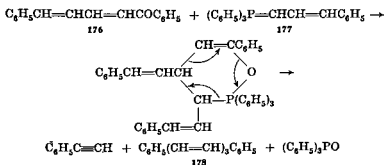
Elimination of acetic acid has also been observed in the reaction of benzyldenetriphenylphosphorane with the ester 173. 1,4-Addition leads to the betaine 174.²⁵³



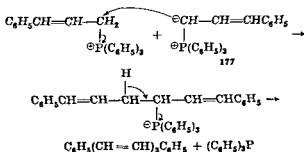
alkylidenephosphorane 175 with methylenecyclohexanone, for which the following mechanism has been assumed.¹⁵⁸



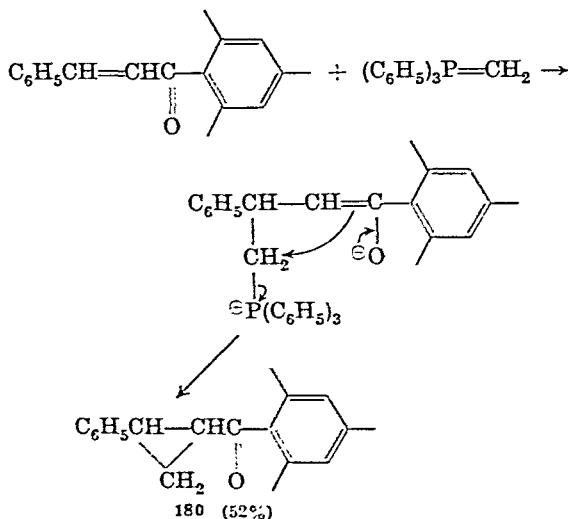
The formation of 1,6-diphenylhexa-1,3,5-triene (178) as a side product in the reaction of ketone 176 with the phosphorane 177 has also been explained on the basis of a 1,4-addition.²¹³



Phenylacetylene could not be detected. An alternative path that has been suggested involves reaction of the ylide 177 with the starting phosphonium salt followed by a Hofmann elimination.¹²



The reaction of methylenetriphenylphosphorane with the sterically hindered mesityl styryl ketone (179) may also be considered as a 1,4-addition. In this reaction, triphenylphosphine rather than triphenylphosphine oxide is eliminated and the cyclopropane 180 is formed.¹³¹

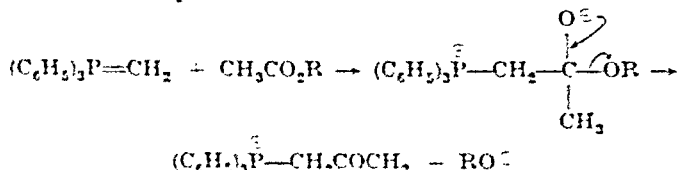


Thus addition to an activated double bond takes place in preference to the Wittig reaction. It is therefore necessary, when the Wittig reaction is used to prepare compounds containing an activated double bond, to avoid an excess of phosphorane in order to prevent subsequent addition of the ylide to the double bond.¹³⁹

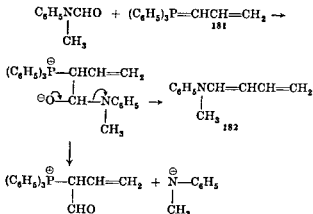
As mentioned previously, α -bromoketones such as phenacyl bromide do not undergo Wittig reactions with alkylidene phosphoranes.¹⁰⁶⁻¹⁰⁸

In compounds that contain both ester and carbonyl groups, the latter react preferentially with Wittig reagents as long as the ylide is not present in excess. The ylide should therefore be added slowly to the carbonyl component.²⁴¹

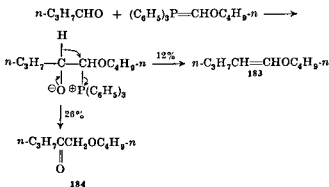
If an excess of alkylidene phosphorane is used in reactions with compounds such as acetylated steroid keto alcohols,^{252,254} the ester group is removed by the ylide by the following process, and the reaction product may have to be reacylated.



A similar side reaction occurred to a lesser extent in the interaction of allylidene triphenylphosphorane (181) with N-methylformanilide. Formation of 1-methylanilino-1,3-butadiene (182) is accompanied by elimination of methylanilide anion.²⁵⁵



An abnormal decomposition of the betaine has also been observed in the reaction of *n*-butoxymethylenetriphenylphosphorane with butyraldehyde, in which formation of the expected 1-*n*-butoxy-1-pentene (183) is accompanied by a hydride shift which gives mostly 1-*n*-butoxypentan-2-one (184).⁸⁷

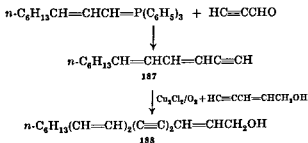


If the oxygen in the betaine may interact with a silicon or a phosphorus atom, attack on silicon occurs preferentially as in the accompanying reaction sequence.¹²³ The ylide 185 so formed reacts with excess

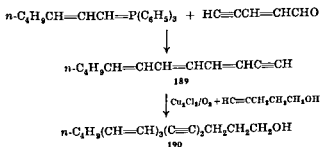
²⁵⁵ Wittig and Sommer, *Ann*, 594, 1 (1955).

suitable method existed for the introduction of a double bond in a precisely defined position. It is therefore not surprising that the Wittig reaction found very early application in the synthesis of naturally occurring polyacetylenic compounds. Bohlmann and collaborators, especially, provided proof for the usefulness of the new method in this area.

The first step in the synthesis of oenanthetol (188), found in hemlock water dropwort (*Oenanthe crocata*) consisted of the preparation of dodeca-3,5-dien-1-yne (187) in 43% yield by means of a Wittig reaction.²⁵⁷ Oxidative coupling of the hydrocarbon 187 with pent-2-en-4-yn-1-ol in the presence of cuprous chloride gave oenanthetol (188) in 14.1% yield in addition to the two symmetrical polyenyne.



The same method was used for the synthesis of cicutol (190), isolated from European water hemlock (*Cicuta virosa*). Oxidative coupling of dodeca-3,5,7-trien-1-yne (189), obtained in 60% yield by a Wittig reaction, gave a mixture of three hydrocarbons from which cicutol (190) could be isolated by chromatography.²⁵⁸ Small amounts of 10-*cis*-cicutol

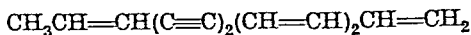
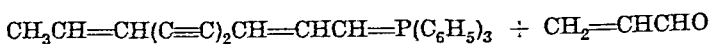


also formed were converted into the all-*trans* form with iodine in petroleum ether.

²⁵⁷ Bohlmann and Vösch, *Chem. Ber.*, **88**, 1245 (1955).

²⁵⁸ Bohlmann and Vösch, *Chem. Ber.*, **88**, 1347 (1955).

Trideca-1,3,5,11-tetraene-7,9-diyne (191), found in a number of coreopsis species, was synthesized by two different methods.²⁵⁹ Path A

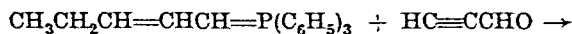


191

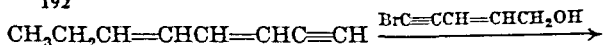


gave only poor yields as compared with about a 50% yield via path B.

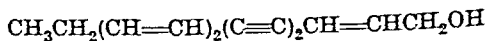
The synthesis of aethusanol B (194), found in fool's-parsley (*Aethusa cynapium* L.), also started with a Wittig reaction.²⁶⁰ Propargyl aldehyde and the phosphorane 192 furnished the intermediate 193 which with



192



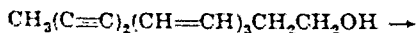
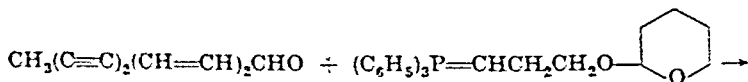
193



194

5-bromopent-2-en-4-yn-1-ol gave aethusanol B (194), identical with one of the three *Aethusa* polyynes.

Hydroxyl groups may also be introduced in the initial stage of a synthesis by using a suitably substituted alkylidene phosphorane, as illustrated by the following two examples. The "chamomilla ester" 195 found in the German chamomile (*Matricaria chamomilla* L.) and in *Matricaria discoidea* DC. was prepared by the following method.⁷¹

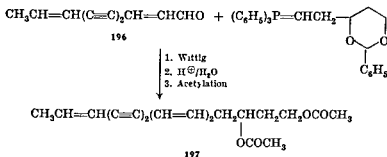


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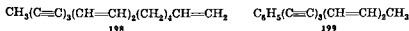
Similarly, matricarianal (196) was converted to "centaur X₂" (197), the principal polyyne of the cornflower (*Centaurea cyanus* L.).⁷²

²⁵⁹ Bohlmann and Mannhardt, *Chem. Ber.*, **88**, 1330 (1955).

²⁶⁰ Bohlmann, Arndt, Bormowski, and Herbst, *Chem. Ber.*, **83**, 951 (1950).

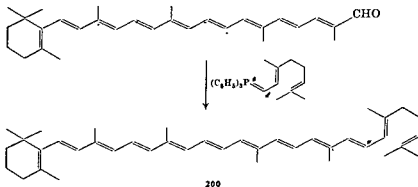


The polyene hydrocarbons 198 and 199 were also synthesized by the Wittig reaction. The former is found in common mugwort (*Artemisia vulgaris*) and in the cornflower (*Centaurea cyanus* L.), the latter in a number of coreopsis species.^{160,261}



Carotenoids and Vitamin A

The synthesis of carotenoids and vitamin A using the Wittig reaction has received particular attention.^{262,263} The synthesis of unsymmetrical carotenoids such as α - and γ -carotene is best carried out using only two components, a polyene aldehyde and an alkylidene phosphorane. Thus γ -carotene (200) can be prepared according to the scheme $\text{C}_{30} + \text{C}_{10} = \text{C}_{40}$.²⁶⁴



200

Another possibility is the combination of a C_{25} -aldehyde with a C_{15} -phosphorane according to the scheme $\text{C}_{25} + \text{C}_{15} = \text{C}_{40}$. Often the

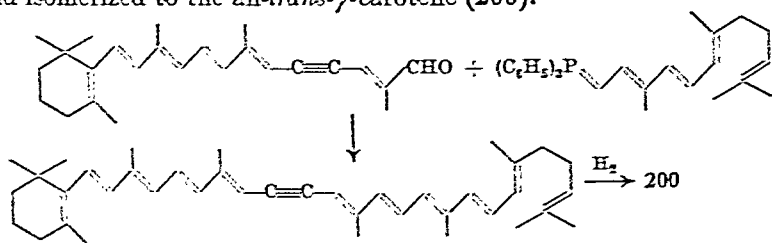
²⁶¹ Bohlmann, *Chem. Ber.*, **88**, 1753 (1955).

²⁶² Pommer, *Angew. Chem.*, **72**, 811 (1960).

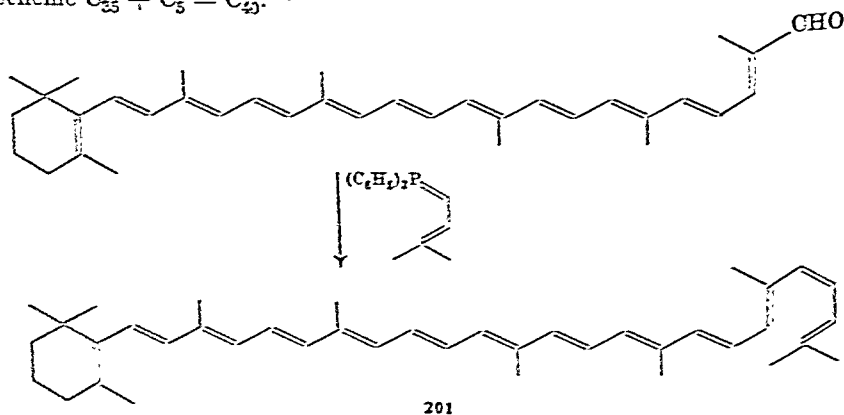
²⁶³ Pommer, *Angew. Chem.*, **72**, 911 (1960).

²⁶⁴ Rügge, Schwietzer, Ryser, Schudel, and Isler, *Helv. Chim. Acta*, **44**, 983 (1961).

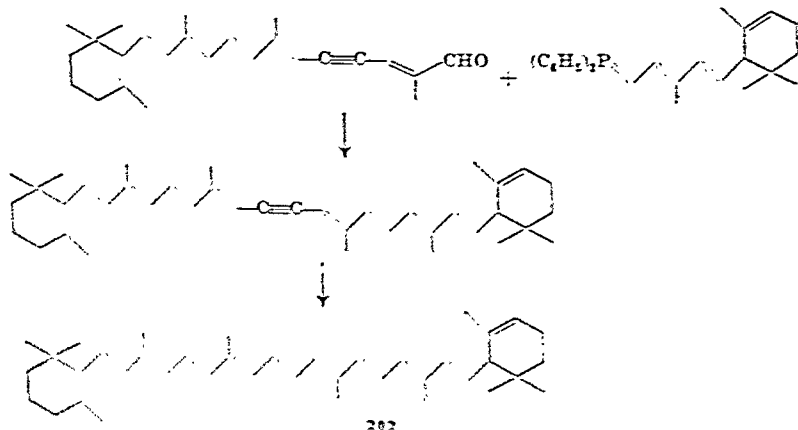
15,15'-dehydro derivative is prepared first, then partially hydrogenated and isomerized to the all-*trans*- γ -carotene (200).²⁵⁴



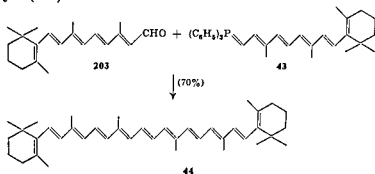
7',8'-Dihydro- γ -carotene (β -zeacarotene), found in corn, was synthesized by the same method.²⁵⁵ 3',4'-Dehydro- γ -carotene (torulin, 201), isolated from *Torula rubra*, on the other hand, was prepared according to the scheme $C_{35} + C_5 = C_{40}$.²⁵⁵



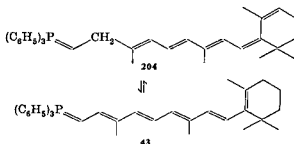
The synthesis of α -carotene (202) followed the scheme $C_{25} + C_{15} = C_{40}$.²⁵⁴



Symmetrical carotenoids such as β -carotene and lycopene may, of course, be prepared by the same method.²⁶⁴ β -Carotene (44) has also been obtained by the scheme $C_{20} + C_{20} = C_{40}$, starting from vitamin A aldehyde (203).²⁶⁸



In place of axerophthylenetriphenylphosphorane (43), the isomeric ylide 204, which is in equilibrium with 43, may also be used.²⁶⁷



The synthesis of symmetrical carotenoids, however, is better carried out by the interaction of dialdehydes with 2 moles of an alkylidene phosphorane or of a bifunctional ylide with 2 moles of an aldehyde. Thus β -carotene (44) is obtained in good yield according to the scheme $C_{15} + C_{10} + C_{15} = C_{40}$ by either path A^{54,268-270} or path B^{80,271} (equations on p. 360). Using path B but starting from vitamin A aldehyde, decapreno- β -carotene is obtained in 38% yield.^{80,271}

The scheme $C_{13} + C_{14} + C_{13} = C_{40}$ illustrates another possible combination.^{209,240,272} In each case, mixtures of the *cis* and *trans* isomers are

²⁶⁸ Pommer and Sarnecki, Ger. pat. 1,068,709 (to BASF) [C.A., 55, 13472i (1961)]

²⁶⁷ Stern, U.S. pat. 2,945,069 (to Eastman Kodak) [C.A., 55, 608e (1961)].

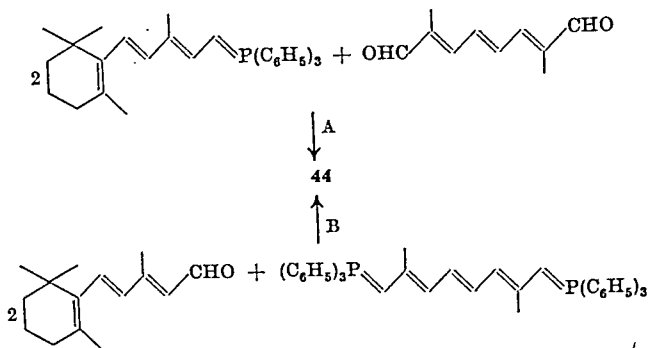
²⁶⁹ Pommer and Sarnecki, Ger. pat. 1,068,703 (to BASF) [C.A., 55, 13473i (1961)]

²⁷⁰ Pommer and Sarnecki, Ger. pat. 1,068,705 (to BASF) [C.A., 56, 1487f (1962)]

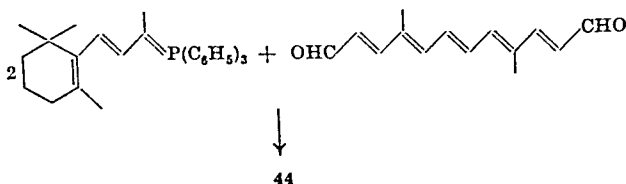
²⁷¹ Pommer and Sarnecki, Ger. pat. 1,068,710 (to BASF) [C.A., 55, 12446g (1961)].

²⁷² Surmatis, Ger. pat. 1,105,869 (to Hoffmann LaRoche), 1959.

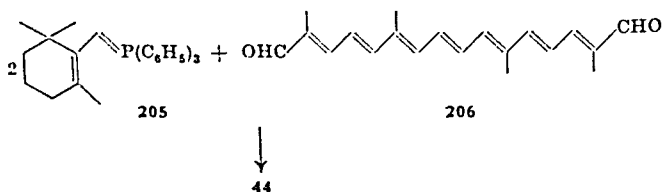
²⁷³ Pommer and Sarnecki, Ger. pat. 1,068,704 (to BASF) [C.A., 55, 13473f (1961)].



obtained. The mixtures can be converted to the all-*trans* form by heating with iodine. The isomerization to the all-*trans* compound can also be effected by nitric oxide.²⁷²



Another possibility for the synthesis of symmetrical carotenoids is expressed by the scheme $\text{C}_{10} + \text{C}_{20} + \text{C}_{10} = \text{C}_{40}$. β -Carotene (44) can thus be obtained from crocetin dialdehyde (206) and 2 moles of β -cyclogeranylidene triphenylphosphorane (205).^{273,274} Good yields were obtained only by using dimethylformamide as the solvent.²⁷⁴



By the same method, lycopene (208), the pigment of the tomato, was prepared starting from geranylidene triphenylphosphorane (207).²⁷⁴⁻²⁷⁷

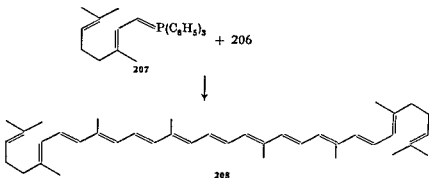
²⁷² Isler, Montavon, Rügge, and Zeller, Ger. pat. 1,017,165 (to Hoffmann-LaRoche) [*C.A.*, 53, 18982b (1959)].

²⁷⁴ Pommer and Sarnecki, Ger. pat. 1,068,707 (to BASF) [*C.A.*, 55, 10499a (1961)].

²⁷³ Isler, Gutmann, Lindlar, Montavon, Rügge, Ryser, and Zeller, *Helv. Chim. Acta*, 39, 463 (1956).

²⁷⁶ Isler, Montavon, Rügge, and Zeller, Ger. pat. 1,038,033 (to Hoffmann-LaRoche) [*C.A.*, 54, 17456h (1960)].

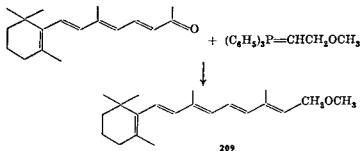
²⁷⁷ Isler, Montavon, Rügge, and Zeller, U.S. pat. 2,842,599 (to Hoffmann-LaRoche) [*C.A.*, 53, 2276h (1959)].



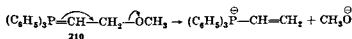
Spirilloxanthene,²⁷⁸ dehydrolycopene, and 1,1'-dihydroxy-1,2,1',2'-tetrahydrolycopene²⁷⁹ were synthesized by essentially the same method.

All these possible synthetic routes may, of course, be applied to the preparation of 15,15'-dehydrocarotenoids. Partial hydrogenation of these compounds leads to the 15,15'-*cis*-carotenoids, which are converted to the all-*trans*-carotenoids on recrystallization or heating in an inert solvent.²⁸⁰

The synthesis of vitamin A and its derivatives is carried out by starting from monofunctional carbonyl compounds and ylides. Vitamin A methyl ether (209) is thus obtained according to the scheme $\text{C}_{18} + \text{C}_2 = \text{C}_{20}$.²⁸¹



The low yield, 10%, is probably due to the instability of the ylide 210.¹³³



The vitamin A skeleton may be obtained by generating any one of the four double bonds in the side chain by combination of suitable aldehydes

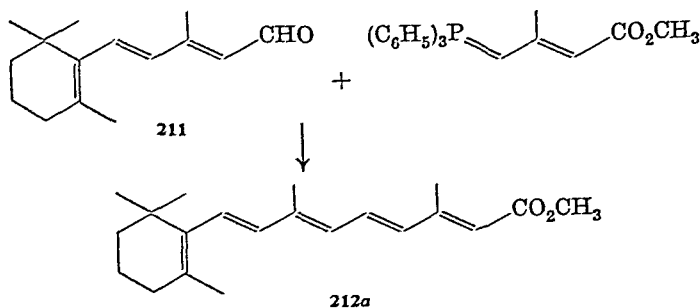
²⁷⁸ Surmatis and Ofner, 142nd Meeting, Am. Chem. Soc., Atlantic City, N.J., Sept. 1962, Abstracts, p. 48Q.

²⁷⁹ Surmatis and Ofner, 142nd Meeting, Am. Chem. Soc., Atlantic City, N.J., Sept. 1962, Abstracts, p. 50Q.

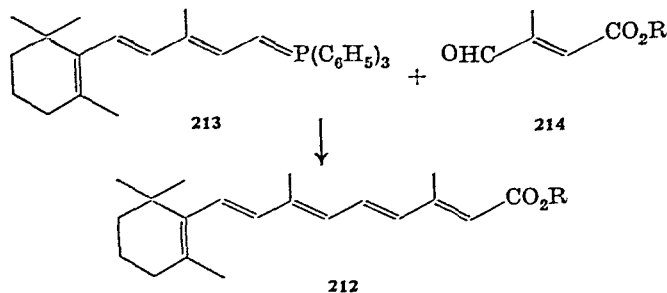
²⁸⁰ Brit. pat. 793,236 (to Hoffmann-LaRoche) [*C.A.*, 54, 627g (1960)].

²⁸¹ Isler, Montavon, Rugg, and Zeller, Ger. pat. 1,017,163 (to Hoffmann-LaRoche) [*C.A.*, 53, 18982c (1959)].

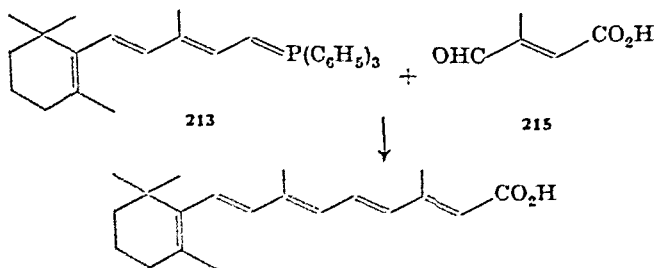
and phosphoranes. The vitamin A acid methyl ester (212a), for example, was prepared from β -ionylideneacetaldehyde (211) according to the scheme $C_{15} + C_5 = C_{20}$.^{55,282}



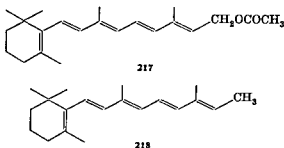
Better yields are obtained by the reaction between the phosphorane 213 and β -formylcrotonic ester (214).^{270,283-286}



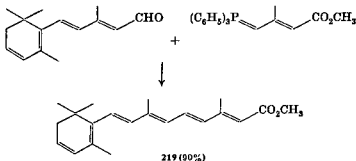
The esters of vitamin A acid (212) are readily saponified to vitamin A acid (216). The latter can be obtained directly from β -formylcrotonic acid (215) and the ylide 213, provided that the free acid is converted to its salt by excess alkali.^{270,284-286}



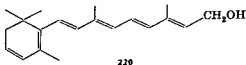
The same scheme was used to synthesize vitamin A acetate (217),^{270,284,285} vitamin A methyl ether (209),^{286a} and desoxy vitamin A or axerophthene (218).^{270,284,285,287}



The synthesis of vitamin A₂ and its derivatives according to the scheme $C_{15} + C_5 = C_{20}$ is illustrated by the preparation of vitamin A₂ acid methyl ester (219).²⁴⁴



Analogously, the vitamin A₂ carbonitrile is obtained in 86% yield. Conversely, β -formylcrotonic ester (214) may also be used as the starting material. The ester of vitamin A₂ acid may subsequently be reduced to vitamin A₂ (220) with lithium aluminum hydride.²⁸⁸

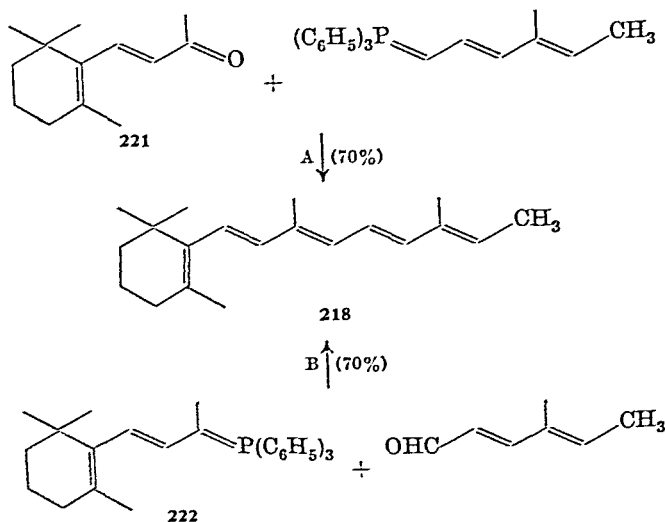


^{244a} Isler, Montavon, Ruegg, and Zeller, Ger. pat. 1,017,164 (to Hoffmann-La Roche) [*C.A.*, 53, 18982d (1959)].

²⁸⁷ Pommer and Wittig, Ger. pat. 1,029,366 (to BASF) [*C.A.*, 54, 22713b (1960)].

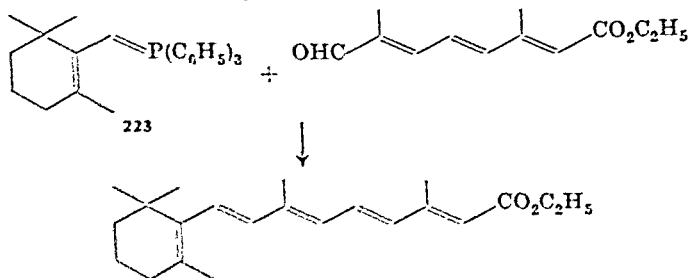
²⁸⁸ Schwietzer, Planta, Ruegg, and Isler, *Helv. Chim. Acta*, 45, 541 (1962).

The synthesis of the vitamin A skeleton according to the scheme $C_{13} + C_7 = C_{20}$ is illustrated by two syntheses of axerophthene (218).^{209,240,287,289}

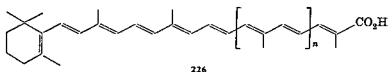
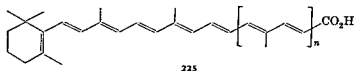
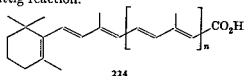


Path A, which starts with β -ionone (221), was also used for the preparation of vitamin A methyl ether (209) and of vitamin A acetate (217).²⁹⁰ Vitamin A acid (216)^{291,292} and its ethyl ester (212b)^{259,292} were obtained in excellent yields via path B starting from β -ionyldenetriphenylphosphorane (222).

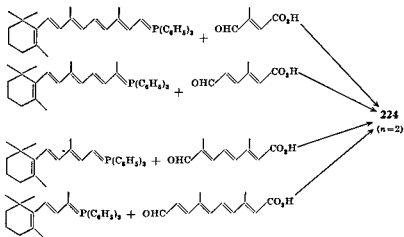
Finally, it may be mentioned that vitamin A acid ethyl ester (212b) was prepared from β -cyclogeranyldenetriphenylphosphorane (223) according to scheme $C_{10} + C_{10} = C_{20}$.²⁹³ Analogously, axerophthene (218) was prepared in 60% yield.²⁹³



Higher homologs (224; $n = 2, 3$) of vitamin A acid and carotene acids of the form 225 and 226 ($n = 0, 1, 2, 3$) have also been synthesized by means of the Wittig reaction.



Homoisoprenovitamin A acid (224; $n = 2$), for instance, was prepared by four different methods.^{240,266,269,270,294}



Of the many syntheses of polyenecarboxylic acids (225 and 226),²⁹⁵⁻²⁹⁸ mention is made only of the preparation of torularhodin (226; $n = 3$),

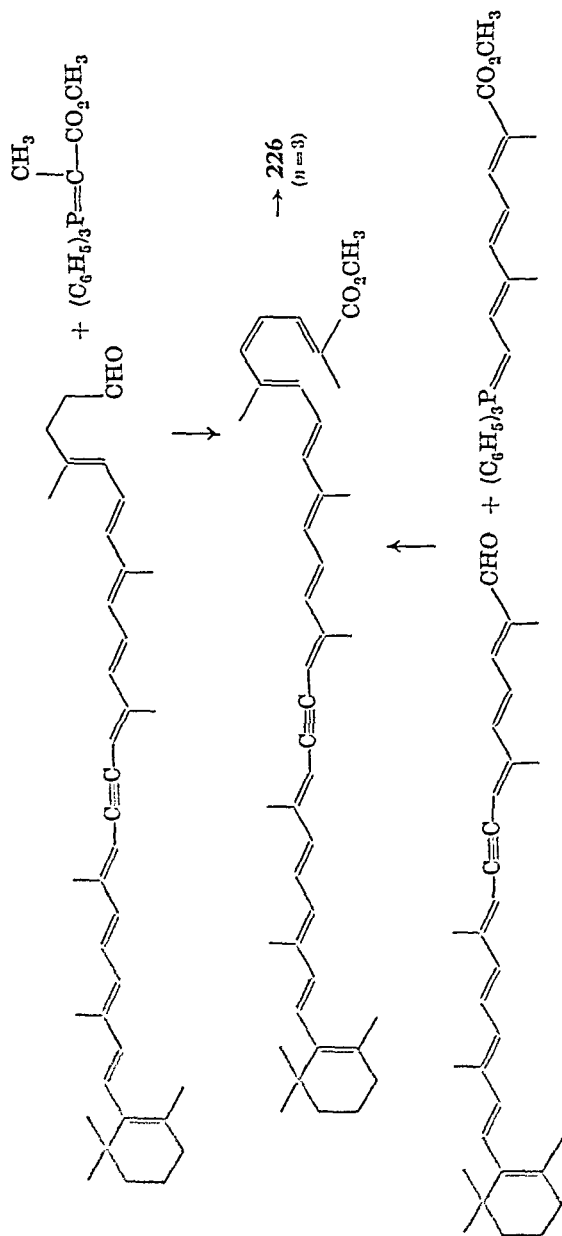
²⁹⁴ Pommer and Sarnecki, Ger. pat. 1,070,173 (to BASF) [C.A., 55, 11332h (1961)].

²⁹⁵ Isler, Guex, Rüegg, Ryser, Saucy, Schwieter, Walter, and Winterstein, *Helv. Chim. Acta*, 42, 864 (1959).

²⁹⁶ Rüegg, Guex, Montavon, Schwieter, Saucy, and Isler, *Angew. Chem.*, 71, 80 (1959).

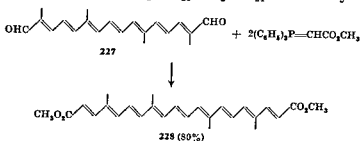
²⁹⁷ Guex, Rüegg, Isler, and Ryser, Ger. pat. 1,098,951 (to Hoffmann-La Roche), 1959; corresponds to Brit. pat. 850,137 [C.A., 55, 17541e (1961)].

²⁹⁸ Guex, Isler, Rüegg, and Ryser, Ger. pat. 1,096,349 (to Hoffmann-La Roche), 1959; corresponds to Brit. pat. 875,713 [C.A., 56, 7372b (1962)].

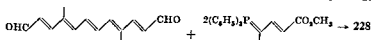


which definitely established the structure of the acid pigment of near yeast (*Torula rubra*).²⁹⁵⁻²⁹⁷ (See p. 366.)

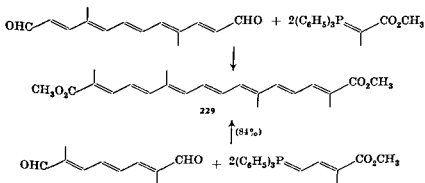
Dieters of norbixin such as methylbixin (228) have been prepared from crocetin dialdehyde (227) and carbalkoxymethylene triphenylphosphoranes according to the scheme $C_2 + C_{20} + C_2 = C_{24}$.^{39,231} Methylbixin can



also be prepared in 76% yield by the scheme $C_5 + C_{14} + C_5 = C_{24}$.^{233,234}



Crocin, the yellow pigment of saffron, is the digentiobiose ester of the C_{20} -dicarboxylic acid crocetin. Diesters of crocetin, such as crocetin dimethyl ester (229), can be synthesized by the same methods as those used for the preparation of norbixin, either according to scheme $C_3 + C_{14} + C_3 = C_{20}$ ^{39,231} or $C_5 + C_{10} + C_5 = C_{20}$.^{232,235}

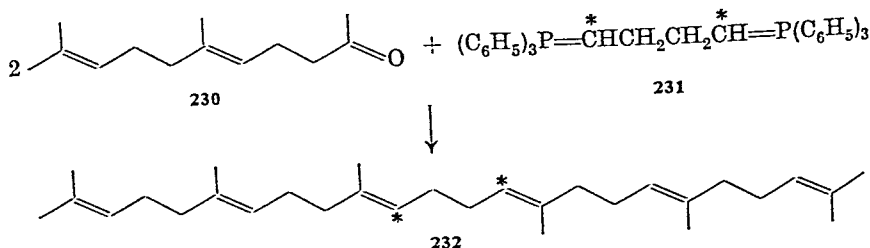


Finally, mention should be made of the synthesis of squalene, a triterpene related to the carotenoids, which is important as an intermediate in the biosynthesis of steroids. Squalene (232) was synthesized by the reaction of geranylacetone (230) with the bis-ylide 231 according to scheme $C_{13} + C_4 + C_{13} = C_{30}$.^{74,299-301}

²⁹⁹ Trippett, *Chem. Ind. (London)*, 1956, 80.

³⁰⁰ Dicker and Whiting, *Chem. Ind. (London)*, 1956, 351.

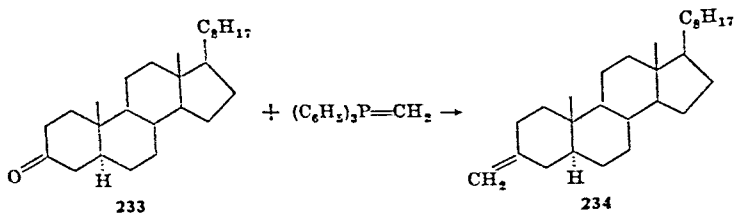
³⁰¹ Dicker and Whiting, *J. Chem. Soc.*, 1958, 1994.



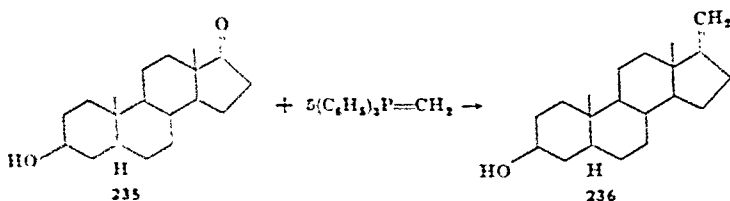
The all-*trans*-squalene (232) was isolated in 12% yield from the mixture of *cis* and *trans* isomers by way of the thiourea clathrate.^{300,301} Analogously, radioactively labeled squalene (¹⁴C-labeled at C₁₁ and C₁₄) was prepared in 50% yield from the ¹⁴C-labeled bis-ylide 231.³⁰²

Steroids and Vitamin D

The method of introducing exocyclic double bonds by means of the Wittig reaction has been used in steroid chemistry. The preparation of 3-methylenecholestane (234) from cholestan-3-one (233) and methylenetriphenylphosphorane was the first instance of a conversion of a steroid ketone to a methylenesteroid by this method.³⁰³ This synthesis was

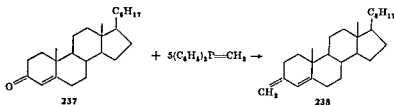


followed by the preparation of a whole series of methylenesteroids in similar fashion, in the course of which it was found that excess methylenetriphenylphosphorane increased the yields.²⁵⁴ 17-Methyleneandrostan-3 β -ol (236) was obtained in 58% yield from androstan-3 β -ol-17-one (235) by using a five-fold excess of methylenephosphorane, but in only 32% yield by employing 3 moles of ylide.²⁵⁴ The yield in this reaction was

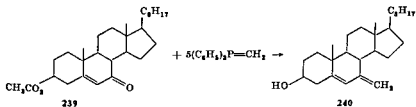


also increased when the 3-hydroxyl group was blocked by conversion to the tetrahydropyranyl ether. The increased yield, however, was offset by losses in the formation and cleavage of the ether.

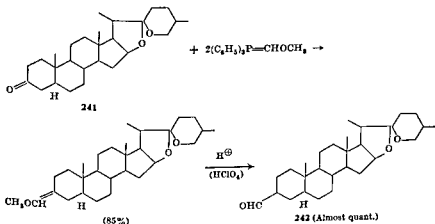
α,β -Unsaturated steroid ketones have also been used as starting materials. Δ^4 -Cholesten-3-one (237), for instance, gives 3-methylene- Δ^4 -cholestene (238) in 80% yield.²⁵⁴



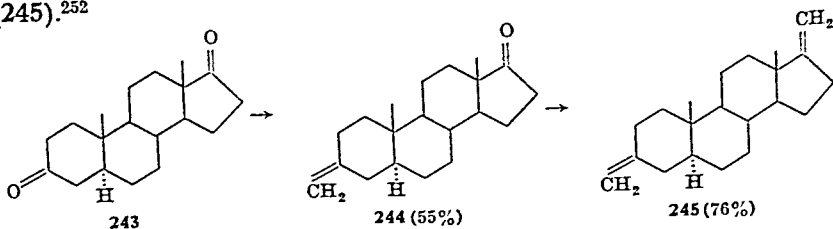
Acetate esters are cleaved by ylides, as illustrated by the preparation of 7-methylenecholesterol (240) from 7-ketocholesteryl acetate (239).²⁵⁴



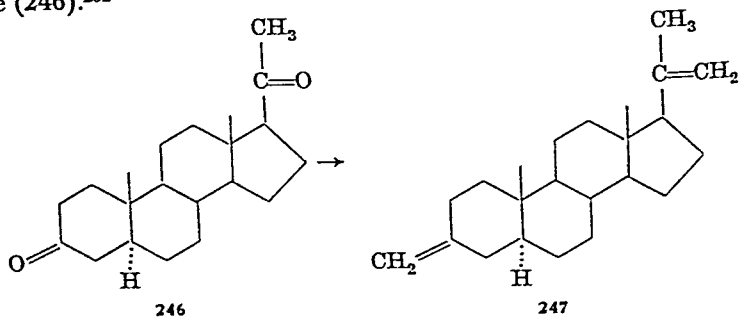
The use of methoxymethylenetriphenylphosphorane in place of methylenetriphenylphosphorane in these syntheses leads to exocyclic enol ethers that can be saponified to the corresponding formyl compounds. An example is the synthesis of 3-formyl-5 α ,22 β ,25D-spirostan-3-one (242) from tigogenone (241).²⁴⁶



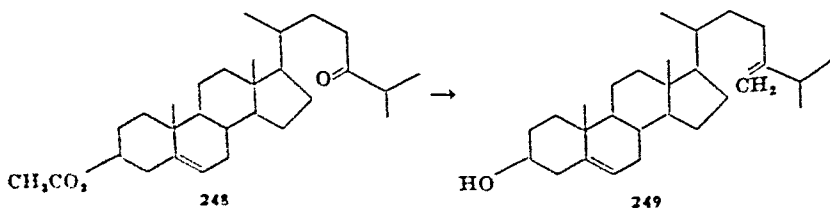
Monomethylene compounds can be isolated from some steroid diketones. The 3-keto group in androstane-3,7-dione (243) is the more reactive, and 3-methyleneandrostane-17-one (244) can be obtained. Further action of methylenetriphenylphosphorane forms 3,17-dimethyleneandrostane (245).²⁵²



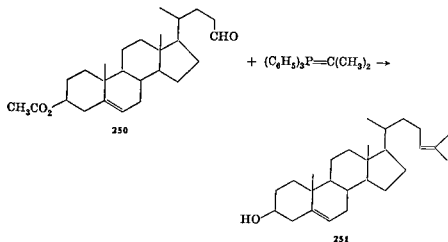
Steroid diketones containing keto groups of comparable reactivities give the dimethylene compounds directly, as illustrated by the formation of 3,20-dimethyleneallopregnane (247) in 75% yield from allopregnane-3,20-dione (246).²⁵²



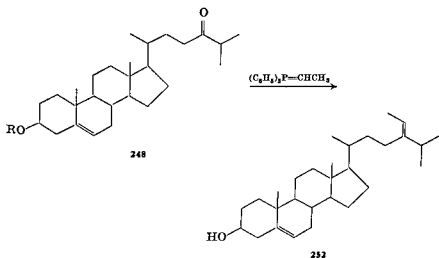
The same method has been used frequently to introduce a methylene group into the side chain of steroids. 24-Ketocholesteryl acetate (248) was converted in 70% yield to 24-methylenecholesterol (249)^{301,304a} which proved to be identical with chalinasterol isolated from sponges and sea anemones, *Zoanthus proteus*, whose structure had been in dispute.³⁰¹



24-Dehydrocholesterol (251), isolated from acorn barnacle (*Balanus glandula*), was synthesized from 3 β -acetoxy-5-cholenaldehyde (250).³⁰⁵



Similarly, 29-isofucoesterol (252) was obtained from 24-ketocholesteryl acetate or 24-ketocholesteryl tetrahydropyranyl ether (248).^{306,307}



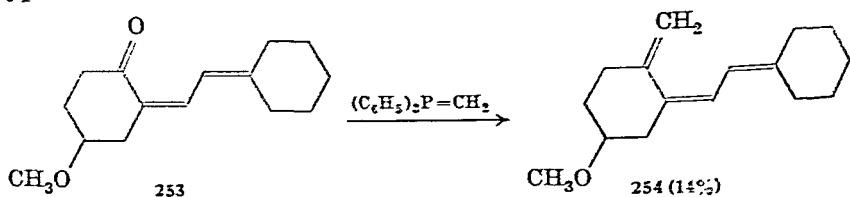
The usefulness of the Wittig reaction for the synthesis of vitamin D was tested first in the preparation of model trienes. The ketone 253

³⁰⁵ Fagerlund and Idler, *J. Am. Chem. Soc.*, **79**, 6473 (1957)

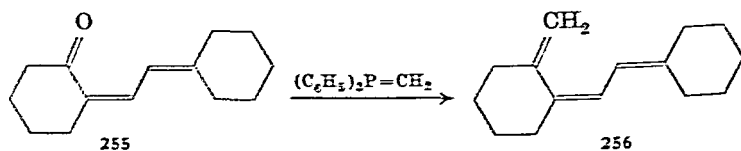
³⁰⁶ Dusza, *J. Org. Chem.*, **25**, 93 (1960)

³⁰⁷ Fagerlund and Idler, *J. Fisheries Res. Board Can.*, **17**, 597 (1960) [*C.A.*, **55**, 2730h (1961)].

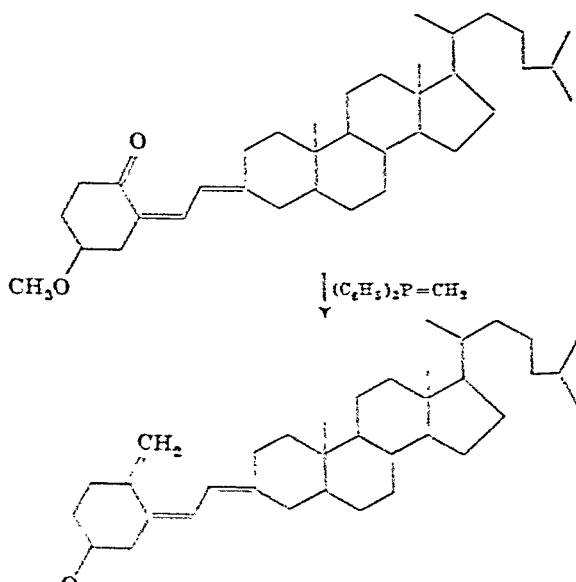
could be converted to the triene 254 which contains a double bond system typical of calciferol.^{303,309}



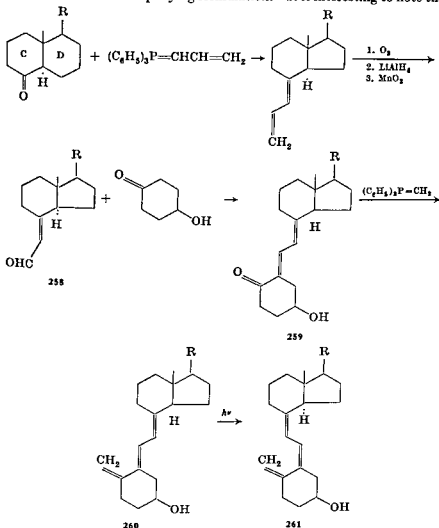
The unsubstituted model substance 256 was prepared analogously from the cyclohexanone derivative 255.^{69,153,154,310,311}



A biologically active homolog of vitamin D₂, 257, whose activity almost reached that of calciferol, was synthesized by the following route.³¹²



vitamins D₂ (calciferol) and D₃, which involved the use of the Wittig reaction in three of the steps.^{70,158,313-321} The final steps of the synthesis are shown in the accompanying formulation. It is interesting to note that



(Vitamin D₂: R = C₁₅H₃₁, —CH(CH₃)CH=CHCH(CH₃)CH(CH₃)₂;
Vitamin D₃: R = C₁₇H₃₃, —CH(CH₃)CH₂CH₂CH₂CH(CH₃)₂)

³¹³ Inhoffen, Kath, and Bruckner, *Angew. Chem.*, **67**, 276 (1955).

³¹⁴ Inhoffen and Irmischer, *Chem. Ber.*, **89**, 1833 (1956).

³¹⁵ Inhoffen, Quinkert, and Hess, *Naturwiss.*, **44**, 11 (1957).

³¹⁶ Inhoffen, Kath, Sticherling, and Bruckner, *Ann.*, **603**, 25 (1957).

³¹⁷ Inhoffen, Quinkert, Schutz, Kampe, and Domagk, *Chem. Ber.*, **90**, 664 (1957).

³¹⁸ Inhoffen, Quinkert, and Schütz, *Chem. Ber.*, **90**, 1283 (1957).

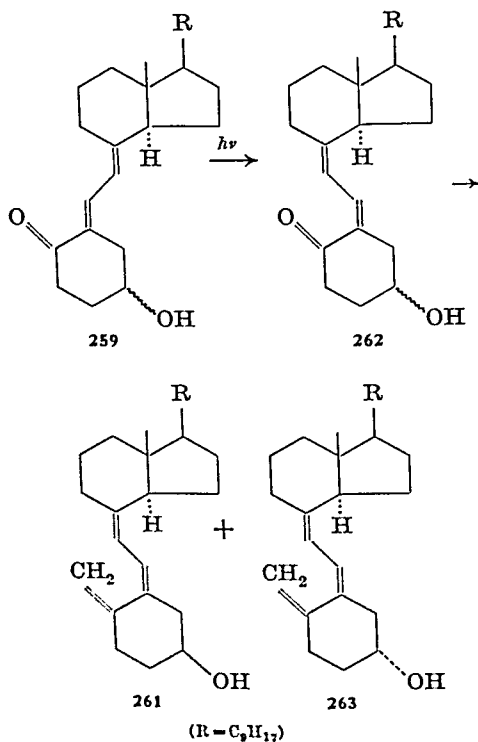
³¹⁹ Inhoffen, Irmischer, Hirschfeld, Stache, and Kreutzer, *Chem. Ber.*, **91**, 2309 (1958).

³²⁰ Inhoffen, Burkhardt, and Quinkert, *Chem. Ber.*, **92**, 1584 (1959).

³²¹ Inhoffen, Irmischer, Friedrich, Kampe, and Borges, *Chem. Ber.*, **92**, 1772 (1959).

in the first step the *trans* configuration of the CD ring system is preserved. The condensation of the aldehyde **258** with *p*-hydroxycyclohexanone gives a mixture of epimers **259** from which the 3β -isomer could be isolated by chromatography. The 3β -5,6-*trans*-vitamin D (**260**) is then converted to vitamins D₂ and D₃ (**261**), respectively, by photoisomerization.

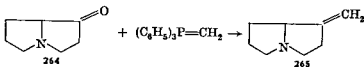
A mixture of calciferol (**261**) and epi-calciferol (**263**) was also obtained by a similar method.^{310,311} The photoisomerization, however, was carried out with the ketone **259**, and the mixture of epimers **262** so obtained was subjected to the Wittig reaction.



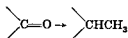
Other Natural Products

The Wittig reaction has also been instrumental in the synthesis of a number of other natural products that do not belong to any of the three groups discussed above. Again, the possibility of introducing exocyclic double bonds by means of methylenetriphenylphosphorane is of decisive importance in these syntheses. The alkaloid 1-methylenepyrrolizidine

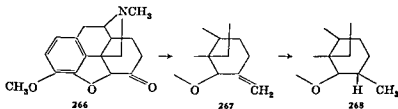
(265), for example, can be synthesized in 63% yield from 1-pyrrolizidone (264).³²²



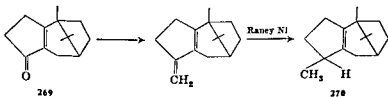
In many cases the exocyclic double bond is subsequently hydrogenated catalytically, so that the over-all effect is the transformation



Thus 6-methyldihydrodesoxycodeine (268) was prepared from dihydrocodeinone (266) by way of 6-methylenedihydrodesoxycodeine (267).¹⁷⁵



Similarly β -patchoulene (270) was synthesized in 38% over-all yield from the ketone 269.¹⁷⁶



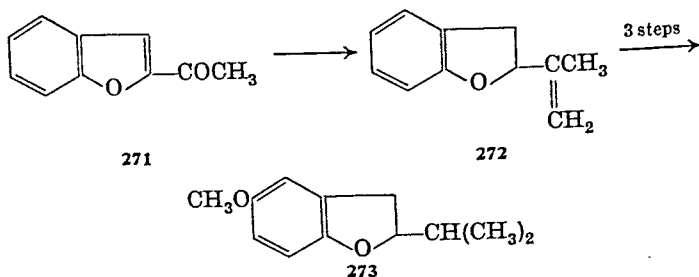
The selective reduction of an exocyclic double bond can also be done with lithium in diethylamine, as illustrated by the synthesis of α -amyrin from glycyrrhetic acid, a β -amyrin derivative of known configuration, which elucidated the structure and configuration of that triterpene.³²³

Dihydrotremetone (273) was synthesized from 2-acetylbenzofuran (271) via 2-isopropenylbenzofuran (272).³²⁴

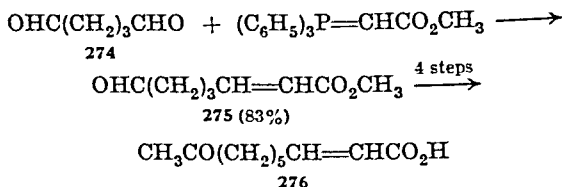
³²² Kochetkov, Likhoshesterov, and Krtsyn, *Tetrahedron Letters*, 1951, 92.

³²³ Corry and Cantrall, *J. Am. Chem. Soc.*, 80, 499 (1958).

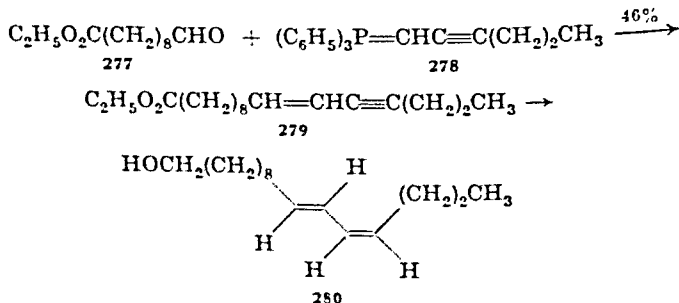
³²⁴ DeGraw and Bonner, *Tetrahedron*, 18, 1311 (1962).



The royal jelly of the honey bee, an α,β -unsaturated acid of structure **276**, was synthesized from glutaraldehyde (**274**).^{228,229} The intermediate 6-(methoxycarbonyl)-5-hexenal (**275**) was converted to 9-oxo-2-decenoic acid (**276**) in four steps. The *trans* isomer (royal jelly) could be isolated in a total yield of 12–15%.

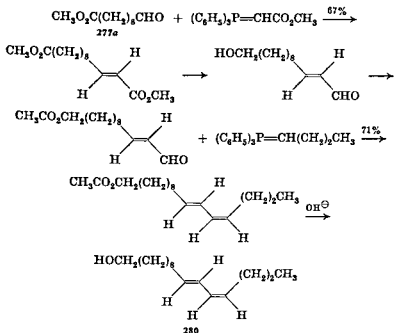


Finally, the important syntheses of insect sex attractants should be mentioned.^{161,325–327} Bombycol, the sex attractant of the female silk moth (*Bombyx mori* L.), was found to be hexadeca-*trans*-10,*cis*-12-dien-1-ol (**280**). All possible *cis-trans* isomers of the hexadecadienol were prepared by different routes using the Wittig reaction. Bombycol itself was synthesized from 9-(ethoxycarbonyl)nonanal (**277**) and the ylide **278** according to the scheme $\text{C}_{10} + \text{C}_6 = \text{C}_{16}$.³²⁵ The *trans* ester was isolated



from the mixture of *cis* and *trans* isomers 279 by means of its urea clathrate and converted to bombycol (280) by partial hydrogenation followed by lithium aluminum hydride reduction.

An alternative route to bombycol (280) from 9-(methoxycarbonyl)-nonanal (277a) that involves two Wittig reactions is shown in the accompanying formulations.^{161,326,327}



By similar methods, the remaining hexadeca-10,12-dien-1-ols,^{161,325-327} as well as other unsaturated aliphatic alcohols, have been synthesized.^{327,328}

The elegant syntheses of oleic acid and other naturally occurring unsaturated fatty acids containing *cis* double bonds have been mentioned previously.¹¹⁴

MODIFIED PROCEDURES AND RELATED REACTIONS

The pyrolysis of β -ketoalkylidene triphenylphosphoranes under certain conditions gives acetylenes by an intramolecular Wittig reaction.^{41,329-331} The reaction is successful only if neither R_1 nor R_2 is

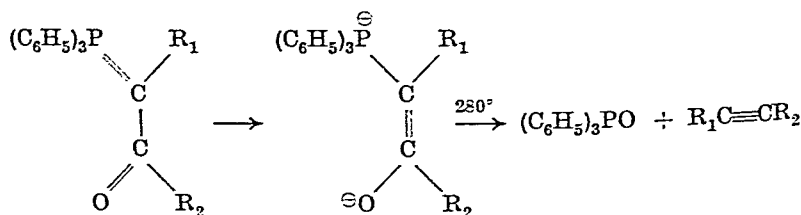
³²⁹ Truscheit and Eiter, Austrian pat. 220,133 (to Farbent. Bayer), 1960.

³³⁰ Gough and Trippett, *Proc. Chem. Soc.*, 1961, 302.

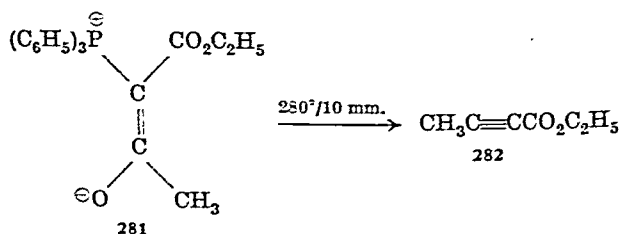
³³¹ Gough and Trippett, *J. Chem. Soc.*, 1962, 2333.

³³² Märkl, *Chem. Ber.*, 94, 3005 (1961)

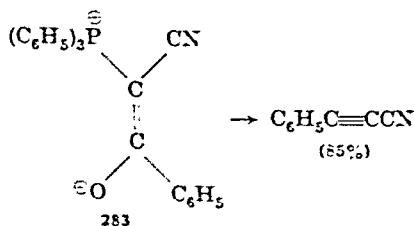
hydrogen. In addition, R_1 or R_2 must be a substituent capable of resonance, such as a phenyl, ester, or nitrile group. If these conditions are



met, acetylenic compounds are obtained in excellent yields. Thus acetylcarbethoxymethylenetriphenylphosphorane (281) could be converted to ethyl 2-butyne-1-carboxylate (282) in 91% yield.³²⁹



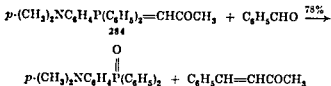
A large number of α,β -acetylenecarboxylic esters has been synthesized in this manner.³³¹ In analogous fashion phenylpropionitrile is formed by pyrolysis of the phosphorane 283.³²⁹



In recent years, practical and theoretical considerations have frequently led to modifications of the Wittig reagents, either by substituting the phenyl groups on phosphorus by other substituents or by replacing the phosphorus by other central atoms.

The use of phosphoranes containing basic substituents such as the acetylmethylene-*p*-dimethylaminophenyldiphenylphosphorane (284) is recommended because the corresponding phosphine oxide can be readily

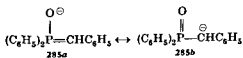
separated from the other reaction products by extraction of the ether solution with dilute acid.¹⁹²



Replacement of the phenyl groups on phosphorus by electron-releasing substituents will result in decreased yields in reactions of normal ylides which are not resonance-stabilized. As discussed previously, the second step of the Wittig reaction, decomposition of the betaine, is rate-determining in these cases, and increased electron density on the phosphorus will have an unfavorable effect. For example, the high yields which can be obtained with methylenetriphenylphosphorane could, in no case, be duplicated with the methylene phosphoranes 66a-f (see p. 311).¹⁵⁵

Aliphatic substituents on phosphorus, such as methyl¹⁰² or cyclohexyl groups,²⁸ also decrease the yields. The situation is different for the resonance-stabilized phosphoranes of the second group, for which the first step of the Wittig reaction is rate-determining. Electron-releasing groups on phosphorus have a favorable effect because they increase the nucleophilicity of the ylides. Thus fluorenylidetri-*n*-butylphosphorane always gives better yields with aldehydes and ketones than does fluorenylidetriphenylphosphorane.²⁹ Increased reactivity has been observed also in other resonance-stabilized phosphoranes in which the phenyl groups on phosphorus had been replaced by alkyl groups.^{28,58,212,222} In addition, alkyl groups on phosphorus influence the stereochemistry of the Wittig reaction, the *trans* isomers being formed almost exclusively.²⁹

Negatively charged oxygen on phosphorus is much more effective than alkyl groups. Metallated phosphine oxides such as 285 are considerably more nucleophilic than the normal alkyldene triphenylphosphoranes, since replacement of a phenyl group by the electron-releasing oxygen results in a strongly increased contribution of the limiting structure 285b to the resonance hybrid.^{223-225,332,333}

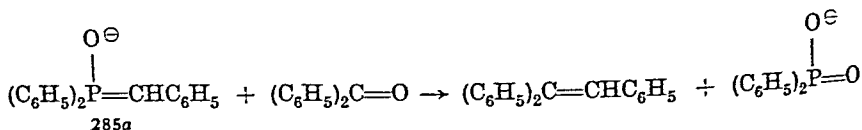


Reaction of benzophenone with 285, for instance, gives triphenyl-ethylene in 70% yield.²²⁴ The other product, diphenylphosphinate ion,

²²² Horner, Hoffmann, and Wippel, Ger. pat. 1,079,030 (to Farb. Hoechst), 1958.

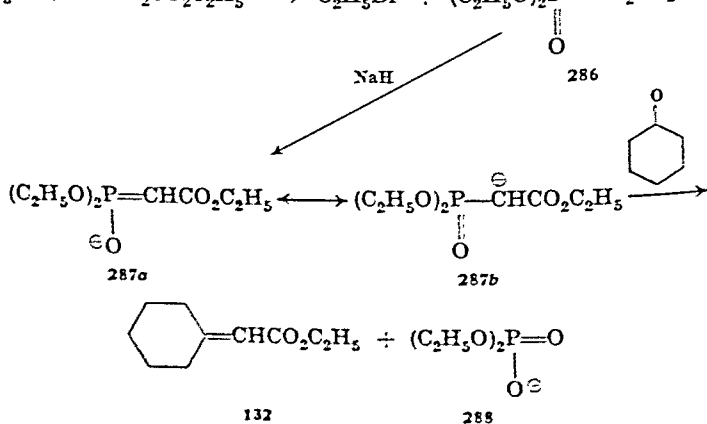
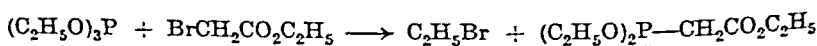
²²³ Horner, Hoffmann, and Klink, Ger. pat. 1,138,757 (to Farb. Hoechst) [C.A., 58, 9143 (1963)].

is water-soluble. Unlike the normal diphenylalkylphosphine oxides,

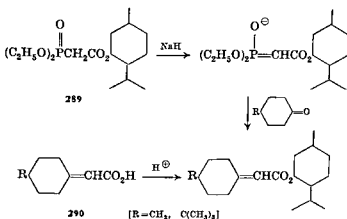


which are readily obtained by the alkaline decomposition of the corresponding triphenylalkylphosphonium salts, phosphine oxides containing groups capable of resonance cannot be prepared by this route. Since these phosphine oxides are not easily obtainable, their reactions have so far attained only theoretical importance. Although normal diphenylalkylphosphine oxides can be metallated and used for the preparation of olefins, they are inferior to the ylides.

Alkylphosphonic acid esters, which can be obtained from triethyl phosphite by an Arbuzow reaction, can in certain cases be metallated and made to react with carbonyl compounds to give olefins in a reaction similar to that of phosphine oxides.^{223-226, 332-334} Thus ethyl bromoacetate reacts with triethyl phosphite to give diethyl carbethoxymethyl phosphonate (286) in good yield. The phosphonate 286 can be converted to the anion 287 with sodium hydride in glycol dimethyl ether. Unlike the corresponding phosphorane, which will react with ketones only under forcing conditions, the anion 287 is strongly nucleophilic and reacts with cyclohexanone at room temperature within a few minutes to give ethyl cyclohexylidene acetate (132) in 70% yield.²²⁶ The diethyl phosphate



The first instance of an asymmetric induction in a Wittig reaction was observed when the reaction was used with the optically active ethyl (*p*-menth-3-yloxy carbonylmethyl)phosphonate (289).³³⁵ The levorotatory isomer of the substituted cyclohexylideneacetic acid 290 was formed predominantly.



Sodium amide^{223,336} and potassium *t*-butoxide^{224,225,332,333} have also been used in place of sodium hydride. Potassium *t*-butoxide has the disadvantage that it leads to resinification with aliphatic ketones such as acetone and cyclohexanone.²²⁵

The metallated diethyl carbethoxymethylphosphonate (287) proved to be superior to carbethoxymethylenetriphenylphosphorane in its reactivity toward other ketones also^{37,103} and has been used for the synthesis of a series of α,β -unsaturated esters.^{228,336,337} α,β -Unsaturated nitriles can be obtained in an analogous manner;^{336,338,339} such nitriles are accessible from cyanomethylenetriphenylphosphorane only if aldehydes are used as the carbonyl component. In general, the phosphonate ester reaction will be the method of choice for the interaction of resonance-stabilized reagents with ketones. In all other cases the normal alkylidene triphenylphosphoranes are to be preferred, in accord with the theory of the mechanism of the Wittig reaction. Alkylphosphonic acid esters, for instance, are completely unsuitable for the preparation of olefins.²²⁵

The phosphonate ester method has found application, particularly in industry,^{262,263} in the synthesis of α,β -unsaturated carboxylic esters,

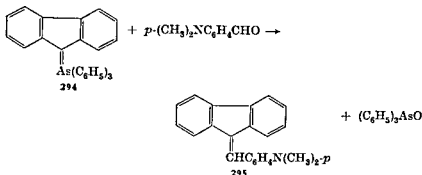
³³⁵ Tömökezy and Janzso, *Chem. Ind. (London)*, 1962, 2085.

³³⁶ Takahashi, Fujiwara, and Ohta, *Bull. Chem. Soc. Japan*, **35**, 1498 (1962).

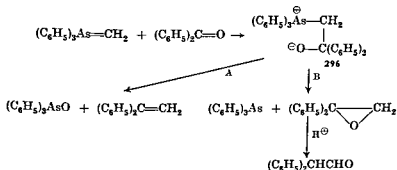
³³⁷ Stiltz and Pommer, Ger. pat. 1,109,671 (to BASF) [*C.A.*, **56**, 8571a (1962)].

³³⁸ Stiltz and Pommer, Ger. pat. 1,108,208 (to BASF) [*C.A.*, **56**, 11422a (1962)].

³³⁹ Pommer and Stiltz, Ger. pat. 1,116,652 (to BASF) [*C.A.*, **57**, 2267d (1962)].

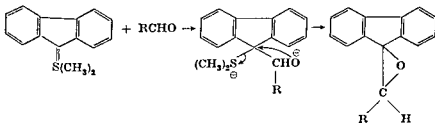


The betaine 296 obtained from methylenetriphenylarsorane and benzophenone can decompose by two different paths.³⁵⁴ After acid hydrolysis,



the products from path A and path B are obtained in about a 1:3 ratio. With antimony as the central atom, the reaction proceeds almost exclusively by path B and 1,1-diphenylethylene and triphenylstibine oxide are formed only in traces.³⁵⁴

Such an abnormal decomposition of a betaine will occur even in a resonance-stabilized ylide if sulfur is used as the central atom.^{355,356} In

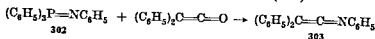


³⁵⁴ Henry and Wittig, *J. Am. Chem. Soc.*, **82**, 563 (1960).

³⁵⁵ Johnson and LaCount, *Chem. Ind. (London)*, 1958, 1440

³⁵⁶ Johnson and LaCount, *J. Am. Chem. Soc.*, **83**, 417 (1961).

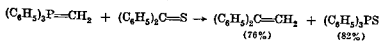
of carbonyl compounds,^{8,363,364} as illustrated by the conversion of diphenylketene to N-phenyldiphenylketene imine (303).



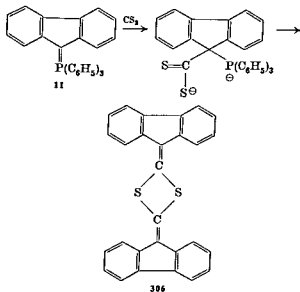
Diethyl phosphoric acid amide anions (304)³⁶⁵ and even N-sulfinyl derivatives (305)³⁶⁶ undergo the corresponding reaction. In the latter case sulfur dioxide is formed as a by-product.



Wittig reagents have also been made to react with a number of compounds that undergo reactions similar to those of carbonyl compounds. For example, thiobenzophenone reacts with methylenetriphenylphosphorane to give 1,1-diphenylethylene.^{13,138}



Carbon disulfide is converted to thioketenes; thus fluorenylidene triphenylphosphorane gives the dimeric thioketene 306 in 68% yield.³⁶⁷



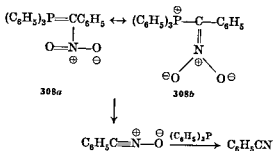
³⁶³ Staudinger and Hauser, *Helv. Chim. Acta*, **4**, 861 (1921).

³⁶⁴ Staudinger and Meyer, *Ber.*, **53**, 72 (1920).

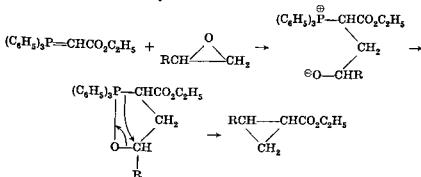
³⁶⁵ Wadsworth, Jr., and Emmons, *J. Am. Chem. Soc.*, **84**, 1316 (1962).

³⁶⁶ Kresze and Albrecht, *Angew. Chem.*, **74**, 781 (1962).

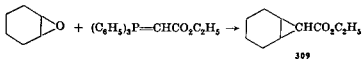
³⁶⁷ Schönberg, Frese, and Brosowski, *Chem. Ber.*, **95**, 3077 (1962).



Finally, mention should be made of the reaction of alkylidene phosphoranes with epoxides for which an intermediate betaine similar to that occurring in the Wittig reaction has been proposed.^{370,371} Styrene oxide and other epoxides react with carbethoxymethylenetriphenylphosphorane to give cyclopropanecarboxylic esters.



Ethyl norcaranecarboxylate (309) is formed in 56% yield from cyclohexene oxide.³⁷¹ Metallated phosphonate esters²²⁶ and phosphine



309

oxides³⁷² undergo analogous reactions.

Methylethylphenylbenzylidenephosphorane (310), on the other hand, reacts with styrene oxide to give mainly benzylacetophenone (311) and only a small amount of 1,2-diphenylcyclopropane. A possible mechanism is shown on p. 388.^{373,374}

³⁷⁰ Denney and Boskin, *J. Am. Chem. Soc.*, **81**, 6330 (1959).

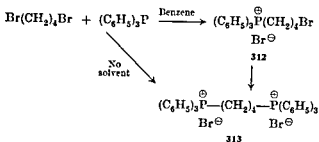
³⁷¹ Denney, Vill, and Boskin, *J. Am. Chem. Soc.*, **84**, 3944 (1962).

³⁷² Horner, Hoffmann, and Toscano, *Chem. Ber.*, **95**, 536 (1962).

³⁷³ McEwen and Wolf, *J. Am. Chem. Soc.*, **84**, 676 (1962).

³⁷⁴ McEwen, Bladé-Font, and Vander Werf, *J. Am. Chem. Soc.*, **84**, 677 (1962).

90% yield.⁵² The bis-phosphonium salt 313 can also be prepared from



the monophosphonium salt 312 and triphenylphosphine either in the melt⁷⁴ or in a different solvent.³⁰¹ In solvents of low polarity, such as benzene, xylene, or diethyl ether, bis-halides generally form the pure monophosphonium salts if they are insoluble in the solvent.³⁷⁵ Strongly polar solvents, such as nitrobenzene, acetonitrile, or dimethylformamide, however, keep the mono salt in solution so that reaction with a second equivalent of triphenylphosphine can take place. For example, reaction of 1,4-dibromobutane with 2 moles of triphenylphosphine in acetonitrile furnishes the bis-phosphonium salt 313 directly in quantitative yield.²²⁵ Suitable choice of solvents will thus make it generally unnecessary to carry out the reaction in the melt. In chloroform, mixtures of mono- and di-phosphonium salts are often formed.

In addition to its polarity, the boiling point of a solvent is also of great importance since it determines the maximum reaction temperature unless the reaction is carried out under pressure. The interaction of ω, ω' -dibromoxylenes with triphenylphosphine proceeds much less readily in ether than in xylene. Some alkyl halides, however, give good yields only if ether is the solvent.²⁴¹ In such reactions it is advantageous to carry out the reaction in a sealed tube at 100–120°.^{71 72 241}

Nitromethane,^{41, 43, 155, 182} formic acid,²²⁵ acetic acid,³⁷⁶ ethyl acetate,^{236, 377} ethanol,^{54, 79} acetone,²⁹ butanone or cyclohexanone,³⁰¹ benzonitrile,¹⁵⁹ toluene,³⁷⁸ and tetrahydrofuran^{69, 209, 287} have been used as solvents. The salts precipitate either spontaneously or on addition of diethyl ether.

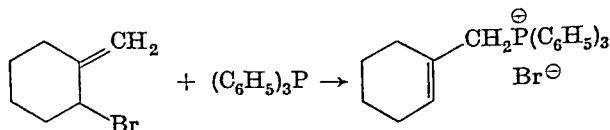
Alkyl bromides may undergo an allylic rearrangement during the quaternization, as illustrated by the reaction of 1-bromo-2-methylene-cyclohexane.^{70, 158}

³⁷⁵ Friedrich and Henning, *Chem. Ber.*, **92**, 2756 (1959).

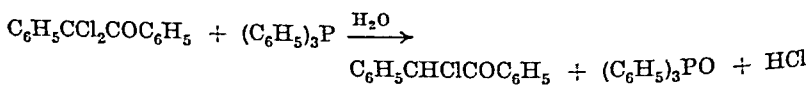
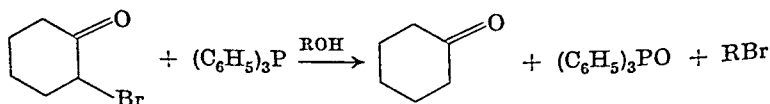
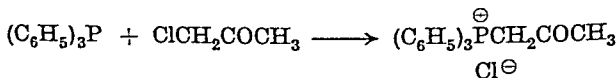
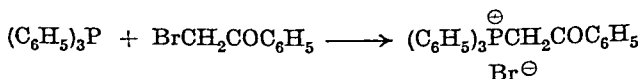
³⁷⁶ Brit. pat. 812,268 (to Hoffmann-La Roche) [*C.A.*, **53**, 18983f (1959)].

³⁷⁷ Isler, Chopard-dit-Jean, Montavon, Ruegg, and Zeller, *Helv. Chim. Acta*, **40**, 1256 (1957).

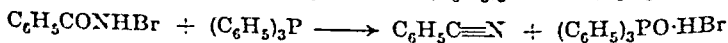
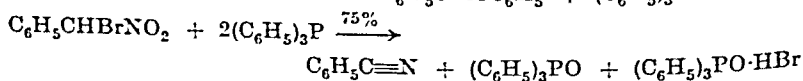
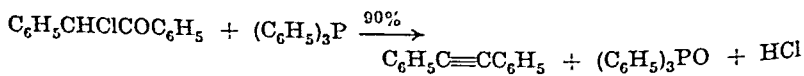
³⁷⁸ Bergmann and Dusza, *J. Org. Chem.*, **23**, 1245 (1958).



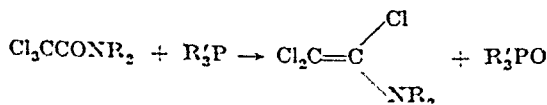
Complications may also occur in the interaction of triphenylphosphine with α -halocarbonyl compounds. Whereas primary α -bromo- and α -chloro-ketones give the desired products,³¹ reaction of secondary and tertiary α -halocarbonyl compounds with triphenylphosphine in the presence of water or alcohol leads to the dehalogenated carbonyl compounds.³⁷⁹⁻³⁸¹



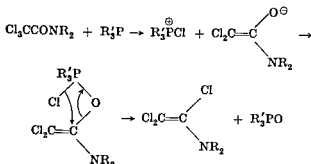
Formation of a triple bond may occur in the absence of water or alcohol.³⁸² Not only α -halo ketones but also 1-bromo-1-nitroalkanes and N-bromoamides react with triphenylphosphine in this way.³⁸²



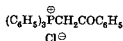
Trichloroacetamides react with phosphines and phosphites to give trichlorovinylamines.³⁸³



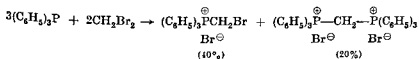
The mechanism of these reactions may involve initial removal of a halogen cation by triphenylphosphine;³⁸⁴ for instance,



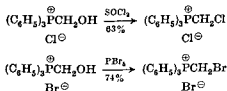
Such a course appears to be followed in the reaction of phenacyl bromide with triphenylphosphine in methanol, whereas phenacyl chloride in methanol undergoes simple displacement of chloride to form the phosphonium salt.³⁸⁵



Halomethylphosphonium salts prepared from dihalomethanes and triphenylphosphine are often contaminated by the bis-phosphonium salt.⁸¹



The pure compounds can be prepared from the corresponding hydroxymethylphosphonium salts with thionyl chloride or a phosphorus pentahalide.^{84,92}

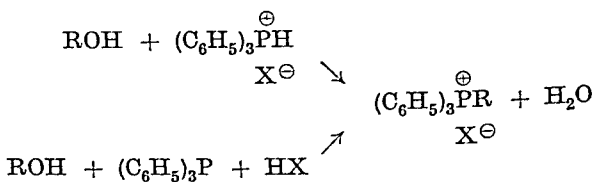


Mention is made of an elegant method for the preparation of phosphonium salts from alcohols, which are made to react either with

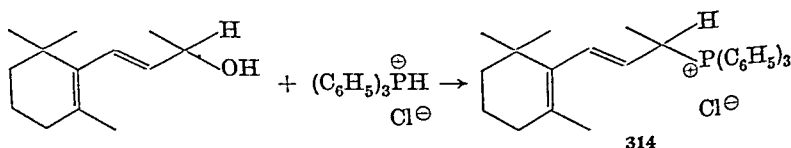
³⁸⁴ Speziale and Smith, *J. Am. Chem. Soc.*, **84**, 1868 (1962)

³⁸⁵ Borowitz and Virkhaus, *J. Am. Chem. Soc.*, **85**, 2184 (1963).

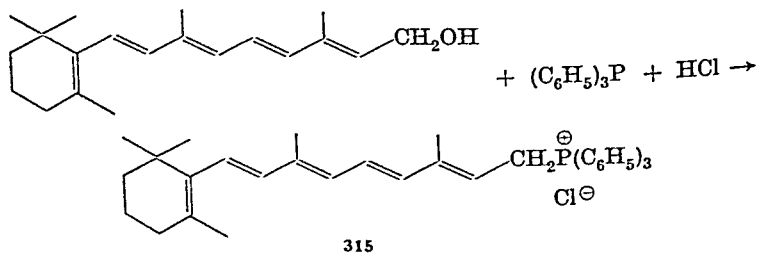
triphenylphosphine hydrohalides or with triphenylphosphine in the presence of proton donors such as hydrogen halides or sulfuric acid.³⁸⁶



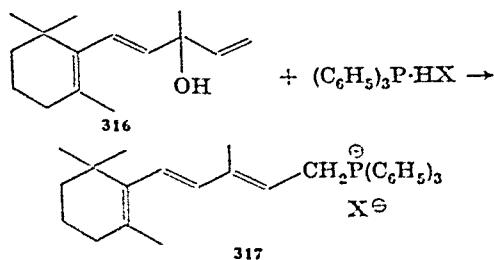
The water is removed either by azeotropic distillation or with silica gel or acetic anhydride. Thus β -ionol and triphenylphosphine hydrochloride react in acetonitrile to give β -ionyltriphenylphosphonium chloride (314).²⁹¹



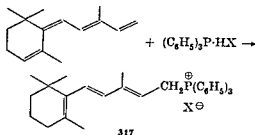
Axerophthyltriphenylphosphonium chloride (315) is obtained in quantitative yield by the reaction of vitamin A with triphenylphosphine and hydrogen chloride in ethanol.^{128,266}



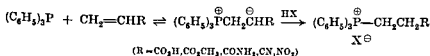
Starting from vinyl- β -ionol (316), (β -ionylideneethyl)triphenylphosphonium halides (317) are obtained by an allylic rearrangement.^{264,268,285,286,294,387}



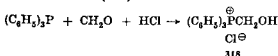
The addition of triphenylphosphine hydrohalides to conjugated systems also leads to phosphonium salts.^{240,266,269,284,292}



Addition may also occur to a monoolefin provided that it is sufficiently activated.³³³



Similarly, the reaction of triphenylphosphine with paraformaldehyde in the presence of hydrogen chloride gives rise to hydroxymethyltriphenylphosphonium chloride (318).⁹²



Thorough washing with benzene usually suffices to purify the phosphonium salts. Purer products are obtained by recrystallization from higher alcohols or tetrahydrofuran or by precipitating the salts from their solutions in chloroform, methanol, or other suitable solvents by addition of ether, acetone, or ethyl acetate. Some phosphonium salts are hygroscopic, or they crystallize with the inclusion of solvent molecules and must be dried well under vacuum before they can be used.

The Wittig Reaction

As a rule, the Wittig reagents are not isolated; immediately following their generation, they are allowed to react with carbonyl compounds in the same reaction vessel.

The Organometallic Method. In this method, phenyllithium or *n*-butyllithium is the usual proton acceptor, and diethyl ether or tetrahydrofuran the solvent. For smaller runs, Schlenk tubes (Fig. 1) have proved to be useful; they are sealed and, if necessary, heated in a water

²⁸² Hoffmann, *Chem. Ber.*, **94**, 1331 (1961).

bath. Larger runs are made in a three-necked flask fitted with stirrer, reflux condenser, addition funnel, and nitrogen inlet tube. If higher reaction temperatures are necessary, the ether must be replaced by a higher-boiling solvent.

The carefully dried and pulverized phosphonium salt is suspended in, for instance, diethyl ether or tetrahydrofuran and an equivalent of a diethyl ether solution of *n*-butyllithium or, preferably, phenyllithium is added under nitrogen. Ylide formation, which usually occurs instantaneously, is evidenced by disappearance of the phosphonium salt with the formation of a red or orange solution.

The ylide solution or suspension so obtained is then treated with the carbonyl compound. As a rule, the phosphonium betaine precipitates immediately. Decomposition of the betaine often occurs in the cold, especially if the newly formed double bond is resonance-stabilized. Heating to 60–70° may be necessary.

When diethyl ether is the solvent, the triphenylphosphine oxide precipitates as a crystalline adduct with 1 mole of lithium halide and may be removed by filtration. The filtrate contains the olefin.

Other solvents which keep triphenylphosphine oxide in solution are best removed by distillation after the reaction is complete. The residue is then extracted with petroleum ether in which triphenylphosphine oxide and lithium halides are insoluble.

The Alkoxide Method. This method uses the alkali metal alkoxides as proton acceptors and the corresponding alcohols as solvents. Either the phosphonium salt and the carbonyl compound are dissolved in alcohol and then treated with one equivalent of an alcoholic solution of the alkali metal alkoxide, or the components are added successively or simultaneously to the alkoxide solution.

With sparingly soluble carbonyl compounds, it is best to dilute the alcohol with a suitable solvent such as methylene chloride or dimethylformamide. Since base is used in the reaction, its consumption may be followed acidimetrically. Aldehydes and ketones that resinify in the presence of alkoxides should not be subjected to the alkoxide procedure but can readily be used in a modified organometallic method.³⁵⁹

The isolation procedure depends on the properties of the resulting olefin. If the olefin is insoluble, it can be isolated by filtration. Triphenylphosphine oxide remains in solution on the addition of up to 40% water and can thus be separated from olefins that are insoluble in

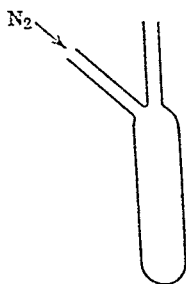


FIG. 1

aqueous alcohol. The solvent may be removed by vacuum distillation and the olefin isolated from the residue by distillation, crystallization, chromatography, or extraction with low-boiling petroleum ether.

Reactions with Resonance-Stabilized Phosphoranes. Acyl-methylene and carbalkoxymethylene triphenylphosphoranes are stable toward water and precipitate as crystalline solids on addition of a base to an aqueous solution of the corresponding phosphonium salt. They may be recrystallized from a mixture of ethyl acetate and petroleum ether. Their reaction with carbonyl compounds may be carried out by heating in a suitable solvent such as benzene or tetrahydrofuran. It is not necessary to isolate the phosphorane; the reaction may be carried out just as well by any of the previously described methods.

EXPERIMENTAL PROCEDURES

Methylenecyclohexane.² Method A (Using *n*-Butyllithium). This preparation is described in *Organic Syntheses*, 40, 66 (1960).

Method B (Using Sodium Hydride in Dimethyl Sulfoxide)⁶³ Sodium hydride (0.10 mole as a 55% dispersion in mineral oil) in a 300-ml. three-necked flask is washed with several portions of *n*-pentane to remove the mineral oil. The flask is then equipped with rubber stoppers, a reflux condenser fitted with a three-way stopcock, and a magnetic stirrer. The system is alternately evacuated and filled with nitrogen; 50 ml. of dimethyl sulfoxide is introduced via syringe, and the mixture is heated at 75–80° for ca. 45 minutes, or until the evolution of hydrogen ceases. The resulting solution of methylsulfinyl carbanion is cooled in an ice-water bath, and 35.7 g. (0.10 mole) of methyltriphenylphosphonium bromide in 100 ml. of warm dimethyl sulfoxide is added. The resulting dark red solution of the ylide is stirred at room temperature for 10 minutes before use.

Freshly distilled cyclohexanone, 10.8 g (0.11 mole), is added to 0.10 mole of methylenetriphenylphosphorane, and the reaction mixture is stirred at room temperature for 30 minutes and immediately distilled under reduced pressure to give 8.10 g. (86.3%) of methylenecyclohexane, b.p. 42°/105 mm., which is collected in a solid carbon dioxide trap

2,2'-Distyrylbiphenyl.¹⁹¹ To a suspension of methylenetriphenylphosphorane, prepared from 0.1 mole of triphenylmethylphosphonium bromide and 0.12 mole of phenyllithium in 200 ml of diethyl ether, is added, under nitrogen, 13.5 g (37.3 mmoles) of 2,2'-dibenzoylbiphenyl, and the mixture is shaken at room temperature for 3 days. The adduct of triphenylphosphine oxide and lithium bromide is removed by centrifugation and the ethereal solution washed with water. The ether is

removed and the residue crystallized twice from ethanol to give 11.4 g. (85.5%) of 2,2'-distyrylbiphenyl, m.p. 100–101°.

***o*-Divinylbenzene.**⁵² Triphenylmethylphosphonium bromide (55 mmoles) is added to a solution of 2.34 g. (60 mmoles) of sodium amide in 300 ml. of liquid ammonia. The ammonia is removed, the residue is dissolved in 200 ml. of absolute diethyl ether and heated under reflux for 30 minutes. To the orange-yellow solution of methylenetriphenylphosphorane is added with stirring over a period of 15 minutes a solution of 3.75g. (28 mmoles) of *o*-phthalaldehyde in 100 ml. of absolute diethyl ether. The mixture is then heated under reflux for 2 hours. The filtered solution is concentrated to 50 ml. and again filtered. From the filtrate, 2.7 g. (75%) of *o*-divinylbenzene, b.p. 75–78°/14 mm., n_D^{20} 1.5765, is obtained by distillation.

4,4'-Divinylbiphenyl.¹⁵⁷ *A.* Biphenyl-4,4'-bis-(methyltriphenylphosphonium chloride). A mixture of 6.3 g. of 4,4'-bis(chloromethyl)biphenyl, 14.2 g. of triphenylphosphine, and 50 ml. of dimethylformamide is heated with stirring under reflux for 3 hours. The phosphonium salt begins to precipitate after about 20 minutes. After the reaction mixture has cooled, the salt is collected by filtration, washed with absolute benzene, and dried under vacuum at 80°. The yield is 85%.

B. 4,4'-Divinylbiphenyl. To a solution of 4 g. of the phosphonium salt in 120 ml. of absolute ethanol are added successively 20 ml. of a 15% solution of formaldehyde in ethanol and 40 ml. of 0.3*M* ethanolic lithium ethoxide. After about 10 minutes the yellow-orange mixture deposits 4,4'-divinylbiphenyl in the form of colorless, shining leaflets. The mixture is diluted with 50 ml. of water and allowed to stand in a refrigerator overnight. The precipitate is collected by filtration and washed with 50% ethanol, giving 4,4'-divinylbiphenyl, m.p. 153°, in 80% yield.

Benzylidenecyclopentane.¹⁵⁵ Triphenylcyclopentylphosphonium iodide (18.3 g., 40 mmoles) in 60 ml. of absolute ether is treated under nitrogen with 40 mmoles of *n*-butyllithium. Solution of the salt and formation of the dark red cyclopentylidenetriphenylphosphorane occur within 2 hours. A solution of 4.3 g. (40.5 mmoles) of benzaldehyde in 10 ml. of absolute ether is added dropwise with cooling, and the mixture is then allowed to stand at about 30° for 10 hours. The clear solution is decanted from the triphenylphosphine oxide, shaken three times with 20-ml. portions of 40% aqueous sodium bisulfite solution, and then washed with water until neutral. Removal of the ether from the dried (calcium chloride) solution followed by vacuum distillation gives 4.1 g. (65%) of benzylidenecyclopentane, b.p. 123–124°/17 mm., n_D^{20} 1.5770.

Lycopene.²⁷⁵ To a suspension of 100 g. of geranyltriphenylphosphonium bromide in 1 l. of absolute ether is added with stirring 200 ml. of a 1*N* ethereal phenyllithium solution. After it has been stirred for 1 hour, the dark red solution of geranylidetriphenylphosphorane is treated within 5 minutes with a solution of 20 g. of crocetinaldehyde in 500 ml. of anhydrous methylene chloride. The mixture is then stirred for 15 minutes at 30° and heated under reflux for 5 hours. Methanol (600 ml.) is added in one portion to the warm solution, which is then cooled to 10° with stirring. The crystalline mass is collected by filtration under carbon dioxide. The crude lycopene is dissolved in 300 ml. of acid-free methylene chloride at a temperature not higher than 40° and then reprecipitated with 500 ml. of methanol. The yield of lycopene, m.p. 172–173°, is 25 g.

***trans*-4-Nitro-4'-methoxystilbene.**¹⁶⁶ Butyllithium (0.85 g, 0.013 mole) is added under nitrogen to a suspension of 4.3 g. (0.01 mole) of *p*-nitrobenzyltriphenylphosphonium chloride in benzene and the mixture stirred for 2 hours. Anisaldehyde (1.63 g, 0.012 mole) is added, and the mixture is stirred at room temperature for 4 hours and then diluted with petroleum ether. The dark precipitate is collected and crystallized from ethanol, giving 2.23 g. (89%) of *trans*-4-nitro-4'-methoxystilbene in the form of yellow crystals, m.p. 131–132.5°

1,4-Diphenyl-1,3-butadiene.⁶⁶ To a solution of sodium ethoxide prepared from 1.5 g. (65.3 mmoles) of sodium and 100 ml. of absolute ethanol is added 18.8 g (48.3 mmoles) of triphenylbenzylphosphonium chloride. The yellow mixture is stirred vigorously for 5 minutes, and an ethanolic solution of 6.6 g. (50 mmoles) of cinnamaldehyde is added dropwise, resulting in a disappearance of the color. In the course of 30 minutes more at room temperature the mixture assumes a tan coloration. The amount of 1,4-diphenylbutadiene, m.p. 150°, isolated is 8.4 g. (84%).

1,2-Distyrylbenzene.^{201a} A. *o*-Xylylene-bis-(triphenylphosphonium bromide). A solution of 66.1 g. (0.25 mole) of *o*-xylylene dibromide and 142.5 g. (0.55 mole) of triphenylphosphine in 500 ml. of dimethylformamide is heated under reflux for 3 hours. The colorless salt, which starts precipitating within 10–15 minutes, is collected by filtration after cooling and washed successively with dimethylformamide and ether. The yield of phosphonium salt, m.p. >340°, is 175.9 g (89%).

B. 1,2-Distyrylbenzene. To a solution of 42.5 g. (0.054 mole) of the bis-phosphonium salt and 12.6 g. (0.119 mole) of benzaldehyde in 150 ml. of absolute ethanol is added 500 ml. of an ethanolic 0.4*M* solution of lithium ethoxide. The mixture is allowed to stand at room temperature for 30 minutes and is then heated under reflux for 2 hours. The orange-red solution is concentrated under vacuum to 100 ml., and 300 ml. of water

is added; the yellow oil that separates is extracted with ether. The ether is removed, and the residual oil is chromatographed on aluminum oxide. Elution with low-boiling petroleum ether and recrystallization from aqueous ethanol give 12.7 g. (84%) of 1,2-distyrylbenzene in the form of colorless needles, m.p. 117–119°.

***p*-bis-(4-Carbomethoxystyryl)benzene.**¹⁹³ To a solution of 54 g. (0.121 mole) of 4-carbomethoxybenzyltriphenylphosphonium chloride and 6 g. (0.0448 mole) of terephthalaldehyde in 600 ml. of ethanol is added 600 ml. of 0.2*M* ethanolic lithium ethoxide. A pale yellow crystalline precipitate forms immediately. Water (600 ml.) is added after 30 minutes, the precipitate is collected by filtration and washed with 200 ml. of 60% ethanol. The yield of *p*-bis-(4-carbomethoxystyryl)benzene, m.p. 290°, is 13 g. (73%).

***p*-bis-(4-Phenylbutadienyl)benzene.** *Method A.* From $p\text{-C}_6\text{H}_4[\text{CH}=\text{P}(\text{C}_6\text{H}_5)_3]_2$.²¹⁰ A solution of lithium ethoxide prepared from 1.74 g. (0.25 mole) of lithium wire, and 1 l. of ethanol is added to a solution of 70 g. (0.10 mole) of *p*-xylylene-bis(triphenylphosphonium chloride) and 35 g. (0.26 mole) of cinnamaldehyde in 250 ml. of ethanol. After the reaction mixture has been left at room temperature for 12 hours, the yellow precipitate is collected by filtration, washed with 300 ml. of 60% ethanol, and dried under vacuum at 70°. The yield is 29–32 g. (87–95%). The crude product may be converted to the all-*trans* isomer with iodine in xylene; after crystallization from dimethylformamide, it melts at 290–293°.

Method B. From *Terephthalaldehyde*.⁶⁶ To a solution of sodium ethoxide prepared from 1 g. (43.5 mmoles) of sodium and 120 ml. of absolute ethanol are added successively 19 g. (41.4 mmoles) of triphenylcinnamylphosphonium bromide and a solution of 3 g. (22.4 mmoles) of terephthalaldehyde in 40 ml. of absolute ethanol. The mixture is heated to 80° for 20 minutes, and the solids are collected by filtration and washed with water and a little ethanol. On crystallization from xylene, 6.0 g. (87%) of *p*-bis-(4-phenylbutadienyl)benzene, m.p. 278–279°, is obtained in the form of yellow needles.

1-Chloro-2,6-dimethyl-1,5-heptadiene.³⁹⁰ To a mixture of 346 g. of triphenylchloromethylphosphonium chloride, 86 g. of piperidine (previously dried over sodium), and 400 ml. of diethyl ether a solution of 1 mole of phenyllithium in 900 ml. of diethyl ether is added dropwise at room temperature over a period of 3 hours. After 1 hour, a solution of 126 g. of 2-methylhept-2-en-6-one in 100 ml. of diethyl ether is added over a period of 2½ hours and the mixture is stirred overnight. The crystalline precipitate is collected by filtration and washed with ether. The ether

¹⁹³ G. Köbrich and W. E. Brockhoff, unpublished research.

and piperidine are removed from the filtrate by distillation, low-boiling petroleum ether is added to the residue, and the triphenylphosphine oxide, which precipitates after a few hours in a refrigerator, is removed. Chromatography on aluminum oxide followed by distillation gives 134 g. (85%) of 1-chloro-2,6-dimethyl-1,5-heptadiene as a colorless liquid, b.p. 69–72°/14 mm., n_D^{20} 1.4687.

Methoxymethylenecyclohexane.^{246,248} To a suspension of 21.25 g. (62 mmoles) of methoxymethyltriphenylphosphonium chloride in 200 ml. of absolute ether is added under nitrogen at room temperature a solution of 60 mmoles of phenyllithium in ether. The reaction is slightly exothermic, and part of the orange-yellow methoxymethylenetriphenylphosphorane precipitates from the dark red solution. After 10 minutes the mixture is cooled to –30°, and 5.88 g. (60 mmoles) of cyclohexanone in 10 ml. of ether is added dropwise. The triphenylphosphine oxide is removed by filtration after 15 hours at room temperature. Distillation of the filtrate gives 5.4 g. (71%) of methoxymethylenecyclohexane, b.p. 74°/48 mm., n_D^{20} 1.4707.

A small sample is heated in ether with 70% perchloric acid, and the hexahydrobenzaldehyde so obtained is converted to its 2,4-dinitrophenylhydrazone, m.p. 168–169°, in 84% yield.

2-Benzyl-5-phenyl-2,4-pentadienol Acid.⁴⁰ *A. Benzylcarbomethoxymethylenetriphenylphosphorane* Benzyl bromide (1.5 ml.) is added to a solution of 5 g. of carbomethoxymethylenetriphenylphosphorane in ethyl acetate, and the mixture is heated under reflux for 5 hours. The precipitate of triphenylcarbomethoxymethylphosphonium bromide (2.69 g., 87%) is removed by filtration, the filtrate is concentrated under vacuum, and the residue is digested several times with ethyl acetate. The yield of ylide, m.p. 186–187°, is 2.8 g (75%).

B. 2-Benzyl-5-phenyl-2,4-pentadienoic Acid A mixture of 10 g. of the ylide, 3.23 ml. of cinnamaldehyde, and 400 ml. of ethyl acetate is heated under reflux under nitrogen for 24 hours. The solvent is removed from the extracts, and the residue is heated under reflux with 10% aqueous methanolic potassium hydroxide for 1 hour. After cooling, a ten-fold amount of water is added, and the remaining triphenylphosphine oxide that precipitates is removed by filtration. The filtrate is concentrated to 100 ml., cooled, acidified with sulfuric acid, and extracted with ether. The dienol acid (5.2 g., 83.3%) is isolated from the dried ether extracts in the form of cream-colored needles, m.p. 180–181°.

Phenylpropionic Acid. *Method A. Via α -Bromocinnamic Acid.*¹¹⁷ (a) *Bromocarbomethoxymethylenetriphenylphosphorane.* To a vigorously stirred solution of 3.35 g. (10 mmoles) of carbomethoxymethylenetriphenylphosphorane in 50 ml. of benzene is added 0.8 g. (5 mmoles) of

bromine. The precipitated phosphonium salt is removed by filtration, and the filtrate is concentrated to dryness. The oily residue solidifies after a short period to give 1.6 g. (77%) of the crystalline bromo ylide.

(b) Phenylpropionic Acid. A mixture of 4.15 g. of the bromo ylide, 1.1 g. of benzaldehyde, and 30 ml. of benzene is heated under reflux for 2 hours. The solvent is removed by distillation, and the residue is heated under reflux with 4 g. of potassium hydroxide in 30 ml. of methanol for 4 hours. The methanol is removed under vacuum, and the residue is extracted with 50 ml. of water. Acidification of the aqueous solution gives a precipitate of 1.2 g. (82% yield) of phenylpropionic acid in the form of fine colorless needles, m.p. 136–138°.

Method B. By Intramolecular Wittig Reaction.^{320,331} (a) Benzoyl-carbomethoxymethylenetriphenylphosphorane. Carbomethoxymethylenetriphenylphosphorane (6.7 g., 20 mmoles) is dissolved in 50 ml. of dry benzene with warming. To the cooled solution is added dropwise with vigorous stirring a solution of 10 mmoles of benzoyl chloride in 10 ml. of benzene. The mixture is left at room temperature for 3 hours, and the precipitated phosphonium salt is removed by filtration. The ylide, m.p. 136–137°, is isolated from the filtrate in 74% yield.

(b) Phenylpropionic Acid. The ylide (1.0 g.) is heated to 220–260° at 0.05 mm. pressure for 15 minutes. The distillate is dissolved in methanol, 3 ml. of concentrated sodium hydroxide solution is added, and the mixture is allowed to stand at room temperature for 24 hours. The methanol is removed under vacuum, and 30 ml. of water is added. The triphenylphosphine oxide is removed by filtration, and the filtrate is acidified with a small amount of concentrated hydrochloric acid, giving phenylpropionic acid, m.p. 135–136°, in 73% yield.

Ethyl Cyclohexylideneacetate.²²⁶ To a suspension of 2.4 g. (0.05 mole) of sodium hydride in 100 ml. of dry glycol dimethyl ether is added dropwise at room temperature 11.2 g. (0.05 mole) of diethyl carbethoxymethylphosphonate. The mixture is stirred for 1 hour until gas evolution stops, and then 4.9 g. (0.05 mole) of cyclohexanone is added dropwise at a rate to keep the temperature below 30°. The mixture is stirred at room temperature for 15 minutes, during which time a viscous oil separates. A large excess of water is added, the ether layer is separated, dried with magnesium sulfate, and distilled under vacuum to give 5.8 g. (70%) of ethyl cyclohexylideneacetate, b.p. 88–90°/10 mm., n_D^{25} 1.4704.

TABULAR SURVEY

Tables I and II list mainly those phosphonium salts, $[(C_6H_5)_3PR]X$, that have been used as starting materials for the Wittig reaction. The

entries are arranged in the order of increasing number of carbon atoms in the alkyl group R. Within each group of salts having the same number of carbon atoms in the alkyl group, the entries follow the Beilstein system.

Tables III, IV, and V also list alkylidene phosphoranes that have not been used in Wittig reactions with carbonyl compounds.

Table VI deals only with those ylides that have been used to prepare olefins. The entries are arranged in the order of increasing number of carbon atoms in the alkylidene portion of the ylide. Under each ylide the olefins prepared from it are listed in the order of increasing number of carbon atoms in the olefin. In this table are also included olefins for whose preparation no details were given in the original reports.

In all the tables, yields are entered only when they were reported in percentages in the original reference.

The literature has been reviewed to January 1, 1963, and some later work has been included. Work reported in patents has been included only when the patent description was detailed. Because of the nature of the topic being reviewed, it is difficult to avoid missing occasional isolated examples of the Wittig reaction. It is hoped that these omissions are few.



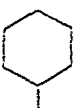
TABLE I
PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES
A. *Monophosphonium Salts*









Carbon Atoms in R	R	and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C ₁	CH ₃		Br	None, 2 days, 20	75	2
				C_6H_6 , 4 days, 20	89	308, 309
	CHCl ₂		Br	None, 4 hr., reflux	—	94
	CH ₂ Br		Br	None, 18 hr., 60	40	81
	CHBr ₂		Br	None, reflux	85	391
	CH ₂ NO ₂		Br	C_6H_6 , 0	—	41
C ₂	C ₂ H ₅		Br	None, 15 hr., 120	96	178
				C_6H_6 , 20 hr., 135	89	164
				$C_6H_5CH_3$, 1 day, 105	90	378
				C_6H_6 , 2 days, 20	—	307
			Br	Xylene, reflux	49	375
	CH ₂ CH ₂ Br		Cl	None, 2 hr., reflux	80	392, 393
	CH ₃ CH ₂ OH		Cl	C_6H_6 , 60 hr., 50	86	92, 247
	CH ₃ OCH ₃		Cl	C_6H_6 , 30 hr., 80	77	92
	CH ₃ SCH ₃		Cl	CHCl ₃ , 5 hr., reflux; 12 hr., 20	—	33, 58
	CH ₂ CHO		Cl	C_6H_6 , 8 hr., reflux	—	243
	CH ₃ CONH ₂		Cl	CH ₃ NO ₂ , 30 hr., reflux	Quant.	41
	CH ₂ CN		Cl	C_6H_6 , 8 hr., reflux	—	42, 243
				CH ₃ NO ₂ , 5 hr., reflux	—	41
			Br	C_6H_6 , 2 weeks, 20	95	43
C ₃	CH(CH ₃) ₂		Br	None, 24 hr., 150	—	305
			I	None, 20 hr., 100	94	178
	CH ₂ CH ₂ CH ₂ Br		Br	C_6H_6 , reflux	63	375

C ₄	CH ₂ CH=CH ₂	Br	C ₆ H ₆ , 12 hr., 20; 1 hr., reflux	92	2
	CH ₂ CH ₂ OCH ₃	Br	C ₆ H ₆ , 8 hr., reflux	80	393
	CH ₂ COCH ₃	Cl	CHCl ₃ , 45 min., reflux	—	31
	CH ₂ CO ₂ CH ₃	Br	C ₆ H ₆ , 12 hr., 20	—	39
	C ₆ H ₅ -n	Br	CH ₂ NO ₂ , 16 hr., reflux	79	182
	(CH ₂) ₄ Cl	Cl	C ₆ H ₆ , 4 hr., reflux	61	130, 375
	(CH ₂) ₄ Br	Br	C ₆ H ₆ , reflux	6	375
	CH ₂ CH=CHCH ₃	Br	C ₆ H ₆ , 14 hr., 130	Quant.	74
	CH ₂ C(CH ₃)=CH ₂	Cl	C ₆ H ₆ , 48 hr., 20	84	181
	CH ₂ CH=CHCH ₂ Br	Cl	C ₆ H ₆ , 30 min., reflux	89	328
	CH ₂ CH ₂ OCOCCH ₃	Br	C ₆ H ₆ , 7 days, reflux	—	304
	CH ₂ CO ₂ C ₂ H ₅	Cl	C ₆ H ₆ , 14 hr., reflux	84-88	230
		Cl	None, 4 hr., reflux	—	392
		Cl-2H ₂ O	C ₆ H ₆ , 5 hr., reflux	—	243
		Br	C ₆ H ₆ , 7 days, 20	89	395
			C ₆ H ₆ , 30 min., reflux	—	3
			C ₆ H ₆ , 12 hr., 20	—	39, 56, 60
			None, 5 min., 80	—	392
			C ₆ H ₆ , 2 hr., 70	—	39, 56, 164, 231
C ₅	CH(CH ₃)CO ₂ CH ₃	Br	Xylene, 15 hr., 160	58	321
	CH ₂ CH ₂ CH(CH ₃) ₂	I	C ₆ H ₅ CH ₃ , 1 day, 115	—	378
	CH ₂ CH=CHC ₂ H ₅	Br	(C ₆ H ₅) ₂ O, 2 days, 20	—	200
	CH ₂ CH=C(CH ₃) ₂	Br	C ₆ H ₆ , 20 hr., 20	—	205
	CH ₂ OC ₂ H ₅ -n	Cl	C ₆ H ₆ , 15 hr., reflux	76	248
	(CH ₂) ₃ OC ₂ H ₅	I	C ₆ H ₆ , 3 hr., reflux	—	138
	CH ₂ CH ₂ CO ₂ C ₂ H ₅	Br	None, 5 min., 100	—	392
	CH(CH ₃)CO ₂ C ₂ H ₅	Br	C ₆ H ₆ , 2 hr., 70	—	39
	CH ₂ CH=CHCO ₂ CH ₃	Br	C ₆ H ₆ , 1 day, 20	96	232, 234, 235

Note: References 391 to 404 are on p. 490.

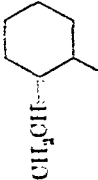
TABLE I—Continued
PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES
A. Monophosphonium Salts—Continued

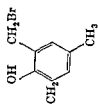
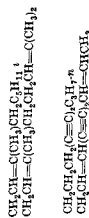

Carbon Atoms in R	R	and in $[(C_6H_5)_3PR]X$	X	Solvent, Temperature, °C.	Yield, %	References
C_5 (<i>contd.</i>)			I	None, 5 hr., 115	40	185
C_6			Br	CH_2Cl_2 , 6 hr., reflux	—	46, 47
	$C_6H_{13}^{n-n}$ $CH_2CH_2-CH(CH_3)H^{n-n}$		Br	—	—	327
	$CH_3CH_2CH_2-C(CH_3)_2$ $(CH_3)_3C(CH_3)-CH_2$		Br	C_6H_6 , 20–30 hr., 20	96	161, 325
	$CH_3CH_2-C(CH_3)_2-CH_2$		I	C_6H_6 , 30 min., reflux	94	326
	$CH_3CH_2-C(CH_3)_2H^{n-n}$		I	C_6H_6 , 3 hr., reflux	88	182
	$CH_3CH_2-CH(CH_3)CH_3$		Br	C_6H_6 , 3 hr., reflux	80	182
			Br	C_6H_6 , 2 days, 20	95	325
			Br	C_6H_6 , 2 days, 20	90	181
			Br	C_6H_6 , 30 min., reflux	Quant.	328
			Br	$CH_3CO_2C_2H_5$, 1 day, 20	—	377
			Br	CH_3CO_2H	—	370
			Br	—	—	286a
			Br	$(C_2H_5)_2O$, 12 hr., 20	—	282
			Br	C_6H_6 , 1 day, 20	77–82	232, 235
			Br	C_6H_6 , 2–3 days, 20	71–77	233, 234
			I	None, 5 hr., 140; 30 hr., 170	72	185

C ₇	$(\text{CH}_2)_6\text{CH}=\text{CH}_2$	Br	$(\text{C}_2\text{H}_5)_2\text{O}$, 2 days, 100	—	160
	$\text{CH}_2\text{CH}=\text{CHC}_6\text{H}_5$	Br	C_6H_6	70	258
	$\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}(\text{OC}_2\text{H}_5)_2$	Br	$(\text{C}_2\text{H}_5)_2\text{O}$, 10 hr., 20; 4 hr., reflux	70	216
	$\text{CH}_2\text{CH}=\text{CHC}(\text{CH}_3)=\text{CHCH}_3$	Br	THF, 12 hr., 20	—	287
	$\text{CH}_2\text{C}\equiv\text{CC}(\text{CH}_3)=\text{CHCH}_3$	Br	C_6H_6 , 2 hr., 40	66	209
		Br	C_6H_6 , 1 day, 20	59	158, 314
	$\text{CH}_2\text{C}_6\text{H}_5$	Cl	None	Quant.	375
	$\text{CH}_2\text{C}_6\text{H}_4\text{Cl}_2$, 2,4	Cl	DMF, 1 hr., 20; 1 hr., 100	—	201
	$\text{CH}_2\text{C}_6\text{H}_4\text{NO}_2$, o	Cl	CHCl_3 , 12 hr., 20	68	220
	$\text{CH}_2\text{C}_6\text{H}_4\text{NO}_2$, p	Br	C_6H_6 , reflux	79	375
C ₈	$\text{CH}_3\text{OC}_6\text{H}_5$	Cl	C_6H_6 , 2 hr., reflux	58	166
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$ 	Br	CHCl_3 , few min., 100	80	220
	$\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}=\text{CHCO}_2\text{CH}_3$	Br	Xylene, 26 hr., reflux	95	210
	$\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{CH}=\text{CHCO}_2\text{CH}_3$	Br	$(\text{C}_2\text{H}_5)_2\text{O}$	80	248
		Br	$(\text{C}_2\text{H}_5)_2\text{O}$, 36 hr., 100	—	71
		Br	$\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$, 1 day, 20	—	236
		Br	C_6H_6 , 12 hr., 20	—	183, 184
		Br	C_6H_6 , 2 days, 20	—	158
		Br	THF, 12 hr., 20	—	69
		Br	THF, 12 hr., 20	—	69

Note: Reference 391 to 404 are on p. 490.

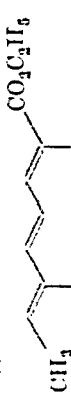






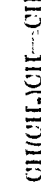
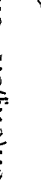

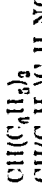
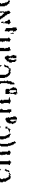



TABLE I—Continued
PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES
A. Monophosphonium Salts—Continued

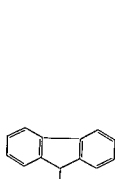
Carbon Atom in R	R and in $[(C_6H_5)_3P^+R]X^-$	N	Solvent, Time, Temperature, °C.	Yield, %	References
C ₈ (contd.)	$CH_3C_6H_4CH_2Br^m$	Br	None	Quant.	375
	$CH_3C_6H_4CH_2Br^p$	Cl	Xylene, 12 hr., reflux	85–90	195
		Br	DMF, 3 hr., reflux	76	210
	$CH_3C_6H_4CH_2Br^m$	Br	C_6H_6 , 8 hr., reflux	92	201a
	$CH_3C_6H_4CH_2Br^p$	Br	Xylene, reflux	38	375
	$CH_3C_6H_4CH_2Br^p$	Br	Xylene, reflux	94	375
	$CH_3C_6H_4CH_2Br^p$	Cl	C_6H_6 , 4 hr., reflux	62	160
	$CH_3OC_6H_4CH_2Br^p$	Cl	$(C_6H_5)_2O$	96	248
	$CH_3C_6H_4CH_2Br^p$	Br	DMF, 30 min., 60	—	201
	$CH_3C_6H_4CH_2Br^p$	Cl	CH_3NO_2 , 2 days, 80	84	396
	$CH_3C_6H_4CH_2Br^p$	Br	$CHCl_3$	—	31
	$CH_3COC_6H_5$	Br	C_6H_6	44	257
	$CH_3CH=CHC_6H_4CH_2Br^m$	Br	$(C_2H_5)_2O$, several days, 20	60	160
C ₉	$CH_3CH=CH(C_6H_5)CH=CH_2$	Br	THF/ $(C_2H_5)_2O$, 12 hr., 20	—	69
					
	$CH_3CH=CHC_6H_5$	Cl Br	Xylene, 12 hr., reflux C_6H_6 , 2 hr., reflux None	91–93 82 Quant.	210 138 375

	Br	C ₆ H ₆ , reflux	97	375
	Br	DMF, 1 hr., 20; 30 min., 60	—	201
	Cl	Xylene, 20 hr., reflux	97	208
	Br	C ₆ H ₆ , 12 hr., reflux	—	330
	Br	C ₆ H ₆ , 3 hr., reflux	69	203
	Cl	Xylene, 1 day, reflux	92	193
		DMF or (CH ₃) ₂ SO, 3 hr., 80	—	199, 200
	Br	C ₆ H ₆ , 2 days, 20	—	276
	Br	C ₆ H ₆ , 2 days, 20	—	275, 276
		C ₆ H ₆ , 6-8 hr., 20	—	397
	Br	C ₆ H ₆ , 30 min., reflux	—	328
		(C ₂ H ₅) ₂ O, 12 hr., 120	96	241
	Br	C ₆ H ₆ , 12 hr., 20	77	259
	Br	C ₆ H ₆ , 2 days, 20	—	275
		C ₆ H ₆ , 1 hr., 60	—	209
	Br	C ₆ H ₆ , 30 min., reflux	Quant.	328
	Br	(C ₂ H ₅) ₂ O, 12 hr., 20	—	181
	Br	(C ₂ H ₅) ₂ O, 1 day, 20	70	180
	Br	Xylene, reflux	93	197
	Br	None, 88 hr., 100	71	202
	Br	C ₆ H ₆ , 2 days, 20	—	275
	Br	C ₆ H ₆ , 1 hr., 60	—	209
	Br	C ₆ H ₆ , 30 min., reflux	Quant.	328
	Br	(C ₂ H ₅) ₂ O, 12 hr., 20	—	181
	Br	(C ₂ H ₅) ₂ O, 1 day, 20	70	180
	Br	Xylene, reflux	93	197
	Br	None, 88 hr., 100	71	202
	Br	C ₆ H ₆ , 2 days, 20	—	275
	Br	C ₆ H ₆ , 1 hr., 60	—	209
	Br	C ₆ H ₆ , 30 min., reflux	Quant.	328

Note: References 391 to 404 are on p. 490.

TABLE I—Continued
 PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES
 A. *Monophosphonium Salts—Continued*

Carbon Atoms in R	R	and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C ₁₂	C ₁₂ H ₂₅ ⁿ		Br	C ₆ H ₆ CN, 3 hr., 140–150	—	159
			Br	CH ₃ CO ₂ C ₂ H ₅ , 1 day, 20	—	236
						
						
						
						
						
						
						
						
						
						
						
						
						
						


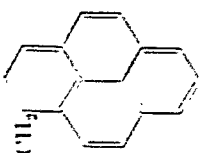
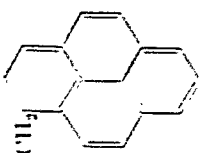
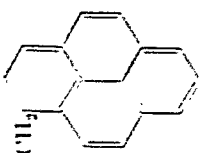
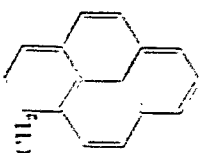
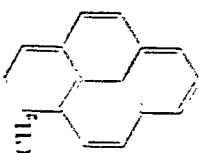
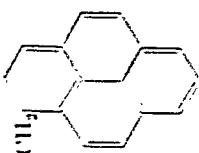


Br	C_6H_6 , 1 hr., reflux CH_3NO_2 , 2 hr., 20	50	88 48
Cl Br	C_6H_6 , 8 hr., 20 $(\text{C}_2\text{H}_5)_2\text{O}^*$	82 7	87 123
Br	C_6H_6 , 12 hr., reflux	—	205
Cl Br	DMF, 12 hr., 20 DMF, C_6H_6 , or $(\text{C}_2\text{H}_5)_2\text{O}$, 1 day, 20	— —	283 54, 283, 287
Br Cl Br Br	$\text{C}_2\text{H}_5\text{OH}$, 1 day, 20 C_6H_6 , reflux Xylene, 10 hr., reflux Xylene, 3-4 hr., reflux Xylene, 4 hr., reflux	— 46 80 87-90 93-95	54 375 195 196 211


Note: References 391 to 401 are on p. 490.

* The halide $(\text{C}_6\text{H}_5)_2\text{C}=\text{CHBr}$ in ether was converted to the Grignard reagent, THF was added, and the solution was added to triphenylphosphine in ether. Oxygen was bubbled through the reaction mixture which was then decomposed with hydrobromic acid.

TABLE I--Continued
 PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHINE AND ALKYL HALIDES
 A. Monophosphonium Salts--Continued


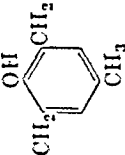
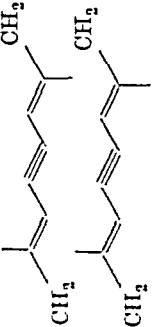
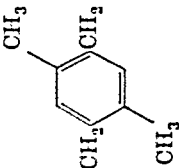
Carbon Atoms in R	R	and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C ₁₆		$CH=CHC_6H_4CH_2C_6H_5$	Br	Nylene, 3-4 hr., reflux	83-85	106
C ₁₇		$CH=CHC_6H_4CH_2C_6H_5$	Br	C_6H_6 , reflux	10	375
C ₁₈		$CH=CHC_6H_4CH_2C_6H_5$	Br	Nylene, 2 hr., reflux	80	197
C ₁₉		$CH=CHC_6H_4CH_2C_6H_5$	Br	C_6H_6 , 12 hr., 20	—	30
C ₂₀		$CH=CHC_6H_4CH_2C_6H_5$	Br	C_6H_6 , 2 hr., 70	—	30
C ₂₁		$CH=CHC_6H_4CH_2C_6H_5$	Br	C_6H_6 , 4 days, 20	—	207
C ₂₂		$CH=CHC_6H_4CH_2C_6H_5$	Br	Nylene, 2 hr., reflux	75-80	108

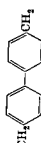

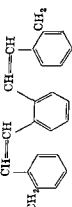
B. *Bis-phosphonium Salts*

Carbon Atoms in R	—R— and in $[(C_6H_5)_3P-R-P(C_6H_5)_3]X_2$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C ₁	CH ₂	Br	None, 150	40	81
C ₂	CH ₂ CH ₂	Br	None, 30 min., 140	82	52
			C ₆ H ₆ , 4 days, reflux	—	210
C ₃	CH ₂ OCH ₂	Br	—	—	190
	CH ₂ CH ₂ CH ₂	Br	None, 30 min., 180	77	52
			DMF, 5 days, 80–90	54	375
			DMF, 3 hr., reflux	94	225
C ₄	CH ₂ COCH ₂	Cl	CHCl ₃ , 2 hr., reflux	8	79
	CH ₂ CH ₂ CH ₂ CH ₂	Cl	None, 25 hr., 160	51	185
		Br	None, 30 min., 250	90	52, 74, 302
			Cyclohexanone, 48 hr., reflux	77	300, 301
	CH ₂ CH=CHCH ₂	Cl	CH ₃ CN, 36 hr., 90	Quant.	225
			Xylene, 60 hr., reflux	65	210
			THF, 16 hr., reflux	94	209
		Br	None, 1 hr., 250	41	230
			DMF	—	212
C ₅	CH ₂ (CH ₂) ₃ CH ₂	Br	CH ₃ CN, 60 hr., 90	54	225
C ₆	CH ₂ (CH ₂) ₄ CH ₂	Br	HCO ₂ H, 12 hr., 110	74	225
	CH ₂ CO ₂ CH ₂ CH ₂ OCOCH ₃	Cl	C ₂ H ₅ OH, 1 day, reflux	98	79
C ₄	CH ₂ CH ₃ 	Br	DMF, 3 hr., reflux	89	201a

Note: References 391 to 404 are on p. 490.

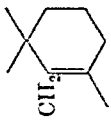
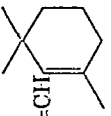
TABLE I—Continued
B. Bis-phosphonium Salts—Continued




Carbon Atoms in R	—R— in $[(C_6H_5)_3P-R-P(C_6H_5)_3]X_2$	X	Solvent, Time, Temperature, °C.	Yield, %	References
C_8 (<i>contd.</i>)		Cl	DMF, 3 hr., reflux	93-98	193
		Br	DMF, 30 min., 150	89	375
			$C_6H_5NO_2$, 30 min., 150	84	375
C_9		Br	DMF, 3 hr., 150	95	375
			$C_6H_5NO_2$, 15 min., 150	94	375
C_{10}		Br	C_6H_6 , 6 hr., 40-45; 12 hr., 20	90	80, 271
		Br	C_6H_6 , 6 hr., 40-45; 12 hr., 20	—	80, 271
		Cl	DMF, 2.5 hr., reflux	94	193

C ₁₄		Cl	DMF, 3 hr., reflux	85	187
C ₁₆		Br	DMF, 3 hr., reflux	75-80	187
C ₂₄		Br	DMF, 16 hr., reflux	56	201 _a

Note. References 391 to 404 are on p. 490.

TABLE II
PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHONIUM HALIDES, $(C_6H_5)_3PHX$, AND ALCOHOLS OR POLYENES
A. *Monophosphonium Salts*

Carbon Atoms in R	R	and in $[(C_6H_5)_3PR]X$	X	Solvent, Time, Temperature, °C.	References
C_4 C_{10}	C_4H_9 ²¹ $CH_2CH=C(CH_3)CH_2CH_2CH=C(CH_3)_2$		Br Cl Br	None DMF, 1 day, 20 THF, 14 hr., 20 DMF, 12 hr., 20	386 274 368 274 279
	$CH_2CH=C(CH_3)CH=CHCH=C(CH_3)_2$		Br		
			Br	THF, 1 day, 20 DMF, 12 hr., 20	368 274
C_{13}	$CH(CH_3)CH=CH$ 		Cl Br	CH_3CN , 1 hr., 20 DMF, 15 hr., 20* DMF, 1 hr., 0*, † Dimethyltetrahydrofuran, 6 hr., 20 DMF, 12 hr., 20* CH_3CN * $CH_3CO_2C_2H_5$, 2 days, 20*	272, 291 240 240 291 240, 292 240 240

C ₁₅		$\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}=\text{CH}$	Cl	THF, 6 hr., 20	285, 387
				THF, 30 hr., 5†	287
				CH ₃ OH, 10 hr., 20	285
				CH ₃ OH, 20 hr., 20†	264, 286
				CH ₃ OH, 18 hr., 20*,†	284
				C ₂ H ₅ OH, 6 hr., 20	268, 285, 294
				CH ₃ CN, 12 hr., 20	270
				CH ₃ CN, 2 days, 20*	269
				DMF, 12 hr., 20	270
				DMF, 3 hr., 20†	270
		$\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}=\text{CH}$	Br	DMF, 12 hr., 10*	284
				DMF, 3 hr., 20*,†	269
				None, 15 hr., 20	285
				CTHF, 60 hr., 20	387
				DH ₃ OH, 36 hr., 20	270
				MF, 12-24 hr., 20	268, 270, 285, 294
				DMF, 36 hr., 20*	269, 284
				DMF, 6 hr., 20	270
		$\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}=\text{CH}$	Cl	CH ₃ OH, 3 hr., 40; 50 hr., 20†	264

Note: References 391 to 404 are on p. 490.

* The polyene corresponding to the alcohol was used.

† Instead of (C₆H₅)₃PtIX, triphenylphosphino and the hydrogen halide, HX, were used.

TABLE II—Continued
 PHOSPHONIUM SALTS FROM TRIPHENYLPHOSPHONIUM HALIDES, $(C_6H_5)_3P^+HX^-$, AND ALCOHOLS OR POLYENES
 A. Monophosphonium Salts—Continued

Carbon Atoms in R	R	and in $[(C_6H_5)_3P^+R]X^-$	X	Solvent, Time, Temperature, °C.	References
C_{13} (contd.)	$CH_3CH_2C(C_6H_5)CH=CH-$ 		Br	CH_3OH , 92 hr., 20	288
	$CH_3CH_2C(C_6H_5)CH=CH-$ 		Cl	CH_3OH , 60 hr., 20†	264
C_{14}	$CH(CH_3)-$ 		Cl	CH_3CN , 2 hr., 20	270
C_{20}	CH_2- 		Cl	DMF, 8 hr., 0 DMF, 12 hr., 10* DMF, 12 hr., 5† C_2H_5OH , 1 day, 20* C_2H_5OH , 1 day, 20†	266 266 266 266 266

B. Bis-phosphonium Salt

Carbon Atoms in R	R	and in $[(C_6H_5)_3P^+R]X^-$	X	Solvent, Time, Temperature, °C.	References
C_4	$CH_3CH=CHCH_3$		Br	C_6H_6 †	386

Note: References 391 to 404 are on p. 490.

* The polyene corresponding to the alcohol was used.

† Instead of $(C_6H_5)_3P^+HX^-$, triphenylphosphine and the hydrogen halide, HX , were used.

TABLE III
ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES
A. *Monophosphoranes*

Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature, °C.	References
C ₁	(C ₆ H ₅) ₂ P=CH ₂	LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	3 hr., 20	2, 303, 304a, 310
			5 days, 20	308, 309
C ₄	(C ₄ H ₉) ₂ P=CHCl (C ₄ H ₉) ₂ P=CHBr (C ₄ H ₉) ₂ P=CHCH ₃		2 hr., reflux	182
			30 min., 20	41, 174
			1 hr., 20	304, 308
			2 hr., 20	130, 252, 254, 319
		LiC ₄ H ₉ , THF	4 hr., 20	183, 317
		NaC(C ₂ H ₅) ₂ , (C ₂ H ₅) ₂ O	30 min., 20	310, 311
		NaNH ₂ , liq. NH ₃		64
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O		52
		Lithium piperide, (C ₂ H ₅) ₂ O		96
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O		84
	(C ₄ H ₉) ₂ P=CHOCH ₃		1 hr., 20	164
			3 hr., 20	178, 307
			1 hr., 0	327
			1 hr., 20	41, 306
				64
		NaC(C ₂ H ₅) ₂ , (C ₂ H ₅) ₂ O		62
		Na(CH ₂ SOCH ₃) ₂ , DMSO		92, 240-248
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	10 min., 20	92
		LiC ₄ H ₉ , THF		92
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	2 hr., -50	92
	(C ₄ H ₉) ₂ P=CHSCH ₃	NaOCH ₃ , CH ₃ OH		92, 247, 248
		NaOC ₂ H ₅ , C ₂ H ₅ OH		92
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O		92
		LiC ₄ H ₉ , THF	15 min., 20	92

Note: References 391 to 404 are on p. 490.

TABLE III—Continued
ALKYLIDENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES
A. Monophosphoranes—Continued





Carbon Atoms in Alkylidene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature, °C.	References
C ₄ (cont'd.)	(C ₄ H ₉) ₃ P=CHCHO	NaOH, H ₂ O		33, 58
	(C ₄ H ₉) ₃ P=CHCONH ₂	(C ₂ H ₅) ₃ N, C ₂ H ₅ OH		33, 58
		NaOH, H ₂ O	0	41
		NaOC ₂ H ₅ , C ₂ H ₅ OH	10 min., 40–50	243
		NaOH, H ₂ O	1 hr., 20	41–43
C ₅	(C ₄ H ₉) ₃ P=CHCN (85)	NaOC ₂ H ₅ , C ₂ H ₅ OH	30 min., 20	113, 243
	(C ₄ H ₉) ₃ P=CHC ₂ H ₅	LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	2 hr., 20	178
	(C ₄ H ₉) ₃ P=CHC ₂ H ₅	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	12 hr., 20	305
	(C ₄ H ₉) ₃ P=CHC ₂ H ₅	LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	2 days, 20	150
				64
	(C ₄ H ₉) ₃ P=CHCH=CH ₂	NaC(C ₆ H ₅) ₃ , (C ₂ H ₅) ₂ O	2–3 hr., 20	2
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	2 hr., 20	259, 318
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O		16
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O		281
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O		33, 58
C ₆	(C ₄ H ₉) ₃ P=CHCOCH ₃ (70)	NaOH, H ₂ O	8 hr., 20	31
		NaOH, H ₂ O	–70	60
		Na ₂ CO ₃ , H ₂ O		39, 56, 297
	(C ₄ H ₉) ₃ P=CClCOCH ₃ (40)	Pyridine, CH ₂ Cl ₂		39, 231, 295, 297
	(C ₄ H ₉) ₃ P=CHCO ₂ CH ₃ (65)	NaOH, H ₂ O	30 min., 20	
		NaOCH ₃ , CH ₂ Cl ₂		
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	2 hr., reflux	182
		LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	2 hr., 20	130
		LiC ₄ H ₉ , pot. ether	1 hr., 20	161, 327
		LiC ₆ H ₅ , (C ₂ H ₅) ₂ O		74
C ₇	(C ₄ H ₉) ₃ P=CH(CH ₂) ₃ Br	NaOC ₂ H ₅ , C ₂ H ₅ OH		74
	(C ₄ H ₉) ₃ P=CHCH=CHCH ₃	LiC ₄ H ₉ , (C ₂ H ₅) ₂ O	10 min. to 3 hr., 20	71, 181, 328, 399

TABLE III—Continued
ALKYLENE PHOSPHORANES PREPARED FROM PHOSPHONIUM SALTS AND BASES
A. Monophosphoranes—Continued


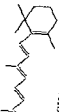




Carbon Atoms in Alkylene Group	Phosphorane (Yield, %)	Base, Solvent	Time, Temperature °C.	References
C ₄ (cont'd.)	(C ₄ H ₉) ₃ P	NaOC ₂ H ₅ , C ₂ H ₅ OH	30 min., 20	325
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	1 hr., 20	181
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	3 hr., 20	328
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	1 hr., 20	377
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , C ₆ H ₆	3 hr., 20	376
	(C ₄ H ₉) ₃ P	NaOC ₂ H ₅ , C ₂ H ₅ OH	4 min., 20	286a
	(C ₄ H ₉) ₃ P	NaC≡CH, DMF	2 hr., 20	282
	(C ₄ H ₉) ₃ P	NaNH ₂ , C ₆ H ₆	1 day, 20	55
	(C ₄ H ₉) ₃ P	NaOH, H ₂ O		55
	(C ₄ H ₉) ₃ P	NaOCH ₃ , CH ₃ Cl ₂		232, 235
C ₇	(C ₄ H ₉) ₃ P	NaOH, H ₂ O		297
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	5-6 hr., 20	233, 234
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O		113, 185
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O		188, 189
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	1 hr., 20	160
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	2 hr., 20	258
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	4 hr., 20	287
	(C ₄ H ₉) ₃ P	NaNH ₂ , C ₆ H ₆	50 hr., 20	287
	(C ₄ H ₉) ₃ P	NaOCH ₃ , DMF		287
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O		209
C ₁₀	(C ₄ H ₉) ₃ P	NaOCH ₃ , CH ₃ OH		210
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	2 hr., 20	314
C ₁₁	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	2 hr., 20	158
	(C ₄ H ₉) ₃ P	LiC ₆ H ₅ , (C ₂ H ₅) ₂ O		

TABLE III—Continued
ALKYLPHOSPHONATES PREPARED FROM PHOSPHONIUM SALTS AND BASES
A. Monophosphonates—Continued

Carbon Atom in Alkylphos- phate Group	Phosphonate (Yield, %)	Base, Solvent	Time, Temperature °C.	Reference
C ₄ (cont'd.)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	60	66
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	195, 196
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	166	146
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	$\text{C}_2\text{H}_5\text{MgBr}$, THF	5 hr., 20	113
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20 min., 20	248
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	KOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	2 hr., 65	201
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOC_2H_5 , DMF	300	390
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	60	60
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOH , H_2O	15 hr., 20	31
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	Na_2CO_3 , H_2O	30 min., -70	60
C ₅	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	Pyridine , CH_3Cl	257	257
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	KOH , $\text{CH}_3\text{OH}/\text{H}_2\text{O}$	10 min., 20	160
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOC_2H_5 , DMF	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOH , H_2O	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	NaOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
C ₆	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{H}$	LiOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$	20	290

C ₁₂	(C ₆ H ₅) ₂ P=CH(CH ₂) ₂ CO ₂ C ₂ H ₅		NaNH ₂ , THF NaOC ₂ H ₅ , THF or DMF		170, 171 170, 171
	(C ₄ H ₉) ₂ P=C(CH ₃)CH=CH 		LiCH ₃ , THF LiC ₆ H ₅ , (C ₂ H ₅) ₂ O C ₄ H ₉ MgBr, THF NaC≡CH, DMF NaNH ₂ , C ₂ H ₅ NaOCH ₃ , C ₂ H ₅ NaOCH ₃ , DMF NaOCH ₃ , DMF	2 hr., 20 15 min., 0 1 hr., 20 12 hr., 20	209 240 240 289 240 240 289 113, 291
	(C ₆ H ₅) ₂ P=C(C ₂ H ₅) ₂		NaC(C ₂ H ₅) ₂ , (C ₂ H ₅) ₂ O NaOC ₂ H ₅ , (C ₂ H ₅) ₂ O NaOC ₂ H ₅ , C ₂ H ₅ OH	30 min. or 3 hr., 20 1 day, 20	64 88 44
	(C ₄ H ₉) ₂ P= 		NH ₂ OH, C ₂ H ₅ OH NaOH, CHCl ₃ /H ₂ O		48 88
C ₁₄	(C ₂ H ₅) ₂ P=C(OC ₂ H ₅) ₂ (C ₄ H ₉) ₂ P=C=C(C ₂ H ₅) ₂		LiC ₆ H ₅ , (C ₂ H ₅) ₂ O LiC ₆ H ₅ , (C ₂ H ₅) ₂ O	-40 1 hr., 20	87 123
C ₁₅	(C ₄ H ₉) ₂ P=CHCH=C(CH ₃)CH ₂ CH 		NaOCH ₃ , DMF	0	265
	(C ₄ H ₉) ₂ P=CHCH=C(CH ₃)CH=CH 		NaOC ₂ H ₅ , DMF		264

Note. References 391 to 404 are on p. 490.

C ₁₇	$(C_6H_5)_3P=CH$ 	NaOC ₂ H ₅ , C ₂ H ₅ OH	20	197
C ₁₈	$(C_6H_5)_3P=CH$ 			
C ₁₉	$(C_6H_5)_3P=CHCO_2C_{10}H_{17-n}$	NaOC ₂ H ₅ , C ₂ H ₅ OH/DMF NaOH, H ₂ O		270 39
C ₂₀	$(C_6H_5)_3P=CHCO_2C_{10}H_{18-n}$	NaOCH ₃ , CH ₂ Cl ₂ NaOCH ₃ , CH ₂ Cl ₂	30 min., 20 30 min., 20	39 39
C ₂₁	$(C_6H_5)_3P=CH$  $(C_6H_5)_3P=CH$ 	LiC ₄ H ₉ , n, (C ₂ H ₅) ₂ O	90 min., 20	267
C ₂₂	$(C_6H_5)_3P=CH$  $[CH_2-CH$  $]_n$	NaOCH ₃ , DMF KOH, CH ₃ OH or C ₂ H ₅ OH LiOC ₂ H ₅ , C ₂ H ₅ OH		266 266

Note: References 391 to 404 are on p. 490

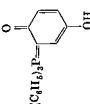
$ \begin{array}{c} \text{CH}_3 \\ \\ (\text{C}_6\text{H}_5)_3\text{P}=\text{CH}-\text{C}_6\text{H}_4-\text{CH}=\text{P}(\text{C}_6\text{H}_5)_2 \\ \\ \text{CH}_3 \end{array} $	$\text{LiOC}_2\text{H}_5, \text{C}_2\text{H}_5\text{OH}$	193, 210
$ \begin{array}{c} (\text{C}_6\text{H}_5)_3\text{P}=\text{CH}-\text{C}_6\text{H}_4-\text{CH}=\text{P}(\text{C}_6\text{H}_5)_2 \\ \\ \text{C}_6\text{H}_5 \end{array} $	$\text{LiOC}_2\text{H}_5, \text{C}_2\text{H}_5\text{OH}$	187
$ \begin{array}{c} (\text{C}_6\text{H}_5)_3\text{P}=\text{CH}-\text{C}_6\text{H}_4-\text{CH}=\text{P}(\text{C}_6\text{H}_5)_2 \\ \\ \text{C}_6\text{H}_5 \end{array} $	$\text{LiOC}_2\text{H}_5, \text{C}_2\text{H}_5\text{OH}$	187, 196
$ \begin{array}{c} (\text{C}_6\text{H}_5)_3\text{P}=\text{CH}-\text{CH}=\text{C}_6\text{H}_4-\text{CH}=\text{P}(\text{C}_6\text{H}_5)_2 \\ \\ \text{C}_6\text{H}_5 \end{array} $	$\text{LiOC}_2\text{H}_5, \text{C}_2\text{H}_5\text{OH}$	201 α

Note. References 391 to 401 are on p. 490.

TABLE IV
ALKYLIDENE PHOSPHORANES PREPARED FROM YLIDES

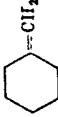
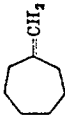


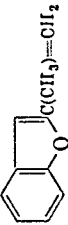
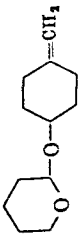
Carbon Atoms in Alkylidene Group	Phosphorane	Reagents (Solvent, Time, Temperature, °C.)	Yield, %	References
C ₃	(C ₂ H ₅) ₃ P---CHCHO	(C ₂ H ₅) ₃ P=CH ₂ + HCO ₂ C ₂ H ₅	07	33
	(C ₂ H ₅) ₃ P---C(CH ₃)CHO	(C ₂ H ₅) ₃ P=CHCHO + C ₆ H ₅ ICl ₂	66	59
	(C ₂ H ₅) ₃ P---CBrCHO	(C ₂ H ₅) ₃ P=CHCHO + Br ₂	83	59
	(C ₂ H ₅) ₃ P---C(CH ₃)CHO	(C ₂ H ₅) ₃ P=CHCH ₃ + HCO ₂ C ₂ H ₅	—	33
	(C ₂ H ₅) ₃ P---CHCOCH ₃	(C ₂ H ₅) ₃ P=CH ₂ + CH ₃ COSC ₂ H ₅	78	32
C ₃	(C ₂ H ₅) ₃ P---C(CH ₃)COCH ₃	(C ₂ H ₅) ₃ P=CHCOCH ₃ + Cl ₂ (CH ₂ Cl ₂ /pyridine, -70)	46	00
	(C ₂ H ₅) ₃ P---CBrCOCH ₃	(C ₂ H ₅) ₃ P=CHCOCH ₃ + C ₆ H ₅ ICl ₂	88	59
	(C ₂ H ₅) ₃ P---CHCO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCOCH ₃ + Br ₂	87	59
	(C ₂ H ₅) ₃ P---C(CH ₃)CO ₂ CH ₃	(C ₂ H ₅) ₃ P=CH ₂ + ClCO ₂ CH ₃	80	111
	(C ₂ H ₅) ₃ P---C(CH ₃)CO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + C ₆ H ₅ ICl ₂ (C ₂ H ₅ , 30 min., 10)	95	117
C ₄	(C ₂ H ₅) ₃ P---CBrCO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + Br ₂ (C ₆ H ₅)	06	59
	(C ₂ H ₅) ₃ P---CHCO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + I ₂ (CH ₃ OH)	87	117
	(C ₂ H ₅) ₃ P---C(CH ₃)CO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + C ₆ H ₅ ICl ₂	94	59
	(C ₂ H ₅) ₃ P---CBrCOC ₂ H ₅	(C ₂ H ₅) ₃ P=CHCOC ₂ H ₅ + Br ₂	97	59
	(C ₂ H ₅) ₃ P---C(CH ₃)COC ₂ H ₅	(C ₂ H ₅) ₃ P=CHCH ₃ + ClCO ₂ CH ₃	95	111
C ₄	(C ₂ H ₅) ₃ P---C(CH ₃)CO ₂ C ₂ H ₅	(C ₂ H ₅) ₃ P=CHCO ₂ C ₂ H ₅ + Cl ₂ (CH ₂ Cl ₂ /C ₂ H ₅ N, -70)	80	00
	(C ₂ H ₅) ₃ P---CBrCO ₂ C ₂ H ₅	(C ₂ H ₅) ₃ P=CHCO ₂ C ₂ H ₅ + Br ₂ (CH ₂ Cl ₂ /NaOH, -70)	09	00
	(C ₂ H ₅) ₃ P---C(CO ₂ CH ₃)C ₂ H ₅	(C ₂ H ₅) ₃ P=CHC ₂ H ₅ + ClCO ₂ CH ₃	88	111
	(C ₂ H ₅) ₃ P---C(COCH ₃)CO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + CH ₃ COCl (C ₆ H ₆ , 3 hr., 20)	97	331
	(C ₂ H ₅) ₃ P---C(CH ₃ CN)CO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + BrCH ₂ CN (CH ₂ Cl ₂ /C ₂ H ₅ , 4-5 hr., reflux)	80	40
C ₄	(C ₂ H ₅) ₃ P---C(COCH ₃)C ₂ H ₅ ⁿ	(C ₂ H ₅) ₃ P=CHC ₂ H ₅ ⁿ + CH ₃ COSC ₂ H ₅	02	32
	(C ₂ H ₅) ₃ P---C(COC ₂ H ₅ ⁿ)CH ₃	(C ₂ H ₅) ₃ P=CHCH ₃ + n-C ₂ H ₅ COSC ₂ H ₅	54	32
	(C ₂ H ₅) ₃ P---C(COCH ₃)C ₂ H ₅ ⁿ	(C ₂ H ₅) ₃ P=CHC ₂ H ₅ ⁿ + CH ₃ CO ₂ CH ₃	90	111
	(C ₂ H ₅) ₃ P---C(CH ₃ CH ₂ ⁿ)CO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + CH ₃ =CHCH ₂ Br (CH ₂ Cl ₂ /C ₂ H ₅ , 4-5 hr., reflux)	93	40
	(C ₂ H ₅) ₃ P---C(COC ₂ H ₅ ⁿ)CN	(C ₂ H ₅) ₃ P=CHCN + n-C ₂ H ₅ COCl	81	330
	(C ₂ H ₅) ₃ P---C(CH ₃ CO ₂ CH ₃)CO ₂ CH ₃	(C ₂ H ₅) ₃ P=CHCO ₂ CH ₃ + BrCH ₂ CO ₂ CH ₃ (CH ₂ Cl ₂ /C ₂ H ₅ , 4-5 hr., reflux)	98	40




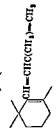


TABLE V
ALKYLIDENE PHOSPHORANES PREPARED DIRECTLY FROM THIOPHENYLPHOSPHINE

Alkylidenephosphorane	Reagents: $(C_6H_5)_3P$ and	Solvent, Time, Temperature, °C.	References
$(C_6H_5)_3P=CH_2$	$CH_2N_2 + Cu^{1+}$	THF	90
$(C_6H_5)_3P=CHCl$	$CH_2Cl_2 + LiC_4H_9 \cdot n$	-60	91, 92
$(C_6H_5)_3P=CF_2$	CF_2Cl_2 or CF_3Br_2	$(C_2H_5)_2O$, -30	95, 96
$(C_6H_5)_3P=CCl_2$	$CHCl_3 + KOC_4H_9 \cdot t$	Pentane, 0-5	98
$(C_6H_5)_3P=CBBr_2$	CCl_4	Heptane, 0	93
	$CHBr_3 + KOC_4H_9 \cdot t$	2 hr., 60	94
	$CBBr_4$	Heptane, 0	98
		CH_2Cl_2	94
			82
		C_6H_6 , 20 hr., 20	99
$(C_6H_5)_3P=CHC_6H_5$	$C_6H_5CHN_2 + Cu^{1+}$	THF	90

Note: References 391 to 404 are on p. 490.

TABLE VI
OLEFINS PREPARED BY THE WITTIG REACTION
A. *Mono-olides as Starting Materials*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
$(C_6H_5)_3P=CH_2$	$n-C_4H_9OCH=CH_2$		$(C_2H_5)_2O$, 12 hr., 20; 3 hr., reflux	113
	$n-C_4H_9C(CH_3)=CH_2$	12	$(C_2H_5)_2O$, 4 hr., 60-75	182
		52	$(C_2H_5)_2O$, 3 hr., 65	2
		5-10		173
	$C_4H_5CH=CH_2$	67	$(C_2H_5)_2O$, 1 hr., 20; 12 hr., 65	2
		63	$(C_2H_5)_2O$, 0 hr., reflux; 2 days, 20	322
	$(CH_3)_3C=CHCH_2CH_2C(CH_3)=CH_2$	10	$(C_2H_5)_2O$, 4 hr., 60-75	182
	$CH_2=C(CH_3)(CH_2)_3C(CH_3)=CH_2$	11	$(C_2H_5)_2O$, 4 hr., 60-75	182
				173
	$C_6H_5C(CH_3)=CH_2$	74	$(C_2H_5)_2O$, 3 hr., 65	2
	$n-C_7H_{15}C(CH_3)=CH_2$	69	$(C_2H_5)_2O$, 1 hr., 20; 5 hr., 65	401
	$C_6H_5CH=CHCH=CH_2$	75	$(C_2H_5)_2O$, 2 hr., reflux	2
	$o-C_6H_4(CH=CH_2)_2$	76	$(C_2H_5)_2O/THF$, 12 hr., 20	52
	$(i-C_4H_9)_2CHCH=CH_2$			402
			THF, 90 min., reflux	324
			$(C_2H_5)_2O$, 1 hr., 20; 2 hr., 65	70

	83	$(C_2H_5)_2O$, 40 hr., 20	174
	61	$(C_2H_5)_2O$, 40 hr., 20	174
	22	$(C_2H_5)_2O$, 70 hr., 60	174
	61	$(C_2H_5)_2O$, 1 day, 60	323
	84	$(C_2H_5)_2O$, 20	1
	62	$CH_3OCH_2CH_2OCH_3$, 4 hr., redox	90
	62	$(C_2H_5)_2O$, 3 hr., 65	2
	6	$(C_2H_5)_2O$, 56 hr., 65	130, 183

References 391 to 404 are on p. 490.

THF, 7 hr., 20

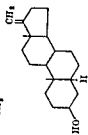
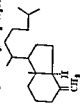
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311

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-ylides as Starting Materials—Continued

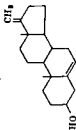
Ylide $C_1 \quad C^1H_3H_3P^+-CH_2^-$ (contd.)	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
		183	$(C_2H_5)_2O$, 12 hr., 20	183
		176	THF	176
		14	$(C_2H_5)_2O$, 3 hr., 65	308, 309
		54	$(C_2H_5)_2O$, 5 hr., 20; 12 hr., 45	138
		186	$(C_2H_5)_2O$, 12 hr., 65	186
		66	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., 65	2
		84	THF, 38 hr., reflux	175



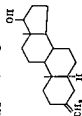
403

67 $(\text{C}_6\text{H}_5)_3\text{O}$, 1.5 hr., 20; 3.5 hr., 65 317

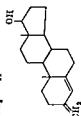
59 THF, 6 hr., reflux 254



36 THF, 6 hr., reflux 254

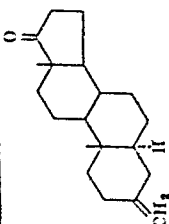
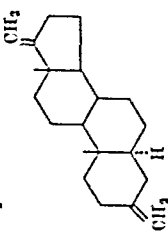
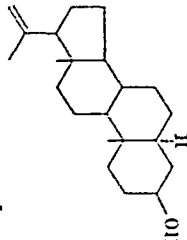
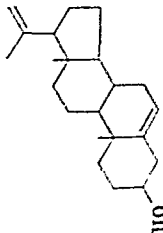


38 THF, 6 hr., reflux 254



57 THF, 6 hr., reflux 254

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-glides as Starting Materials—Continued

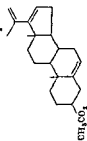
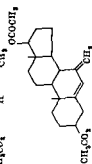
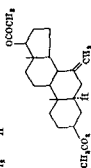
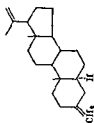
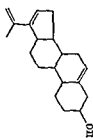
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
C ₁ (C ₆ H ₅) ₃ P=CH ₂ (contd.)		55	THF, 6 hr., reflux	252
		70	THF, 6 hr., reflux	252
		55	THF, 6 hr., reflux	252
		35	THF, 6 hr., reflux	254, 400

75 THF, 6 hr., reflux

17 THF, 6 hr., reflux

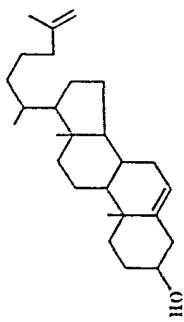
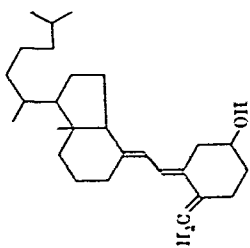
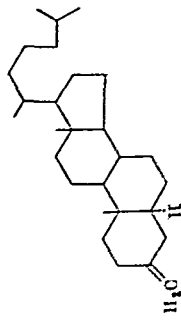
26 THF, 6 hr., reflux

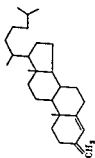
48 THF, 6 hr., reflux



Note: References 391 to 404 are on p. 430.

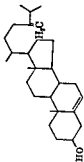
TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-ylides as Starting Materials—Continued

Ylide $(C_4H_9)_3P \cdot CH_2$ (contd.)	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
	$(C_4H_9)_3CCH_2CH(CH_3)C(CH_3)=CH_2$ 	71	$(C_2H_5)_2O$, 8 hr., 60	2
		53	$(C_2H_5)_2O$, 1 hr., 20; 5 hr., 65	304a, 398
		55	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., reflux	319
		60	$(C_2H_5)_2O$, 12 hr., reflux THF, 6 hr., reflux	303 254



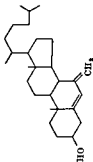
50 THF, 6 hr., reflux

254



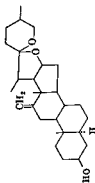
(C₂H₅)₂O, 1 hr., 20; 3 hr., 65

304



40 THF, 6 hr., reflux

254

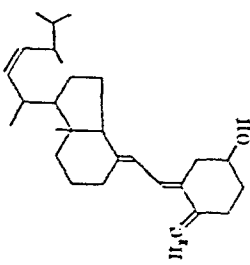
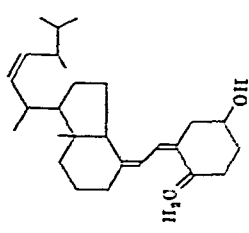
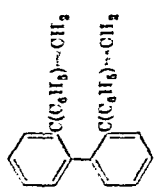


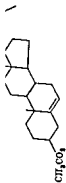
51 THF, 6 hr., reflux

254

Note: References 391 to 404 are on p. 490.

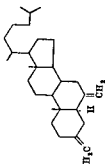
TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-phides as Starting Materials—Continued

Ylide $C_1 (C_6H_5)_2P=CH_2$ (contd.)	Product	Yield, %	Solvent, Time, Temperature, °C.	References
		46	$(C_3H_7)_2O$, 1 hr., 20; 3 hr., reflux	310
			THF, 7 hr., 20	310, 311
		80	$(C_3H_7)_2O$, 3 days, 20	101



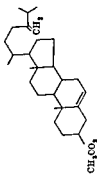
54 THP, 6 hr., reflux

252



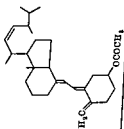
51 THP, 6 hr., reflux

252



71 (C₂H₅)₂O, 1 hr., 20; 5 hr., 65

304a



65 (C₂H₅)₂O, 1 hr., 20; 3 hr.,
reflux

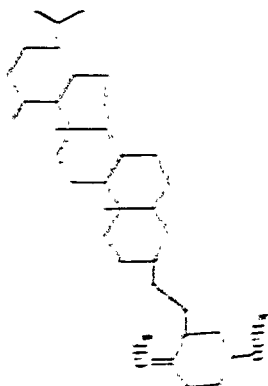
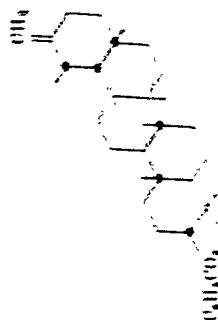
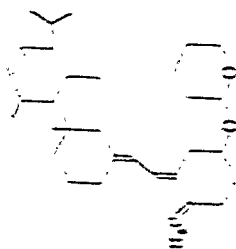
316




Note: References 391 to 404 are on p. 490.

TABLE VI Continued
 OLAPINS PREPARED BY THE WITTIG REACTION
 A. Monophtenyl-Stilbenol Materials Continued

Yield, %	Solvent, Temp., Temperature, °C.	Reduction
20	(C ₁₀ H ₈) ₄ O, 60 min., 60; 16 hr., 313	313
23	(C ₁₀ H ₈) ₄ O	313

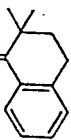
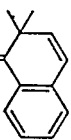
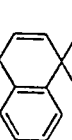
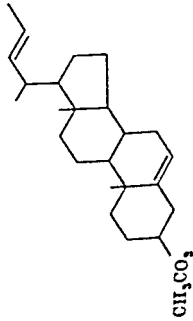
Yield
 C₁₀H₈(C₁₀H₈)₄O (cont.)

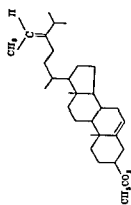


$(C_6H_5)_2P=CF_3$ $(C_6H_5)_2P=CHCl$	$C_6H_5CH=CF_3$ $(C_6H_5)_2C=CHCl$ $n-C_6H_5(CH_2)_2=CHCl$	26 27	THF, 6 hr., reflux THF, 6 hr., reflux	94 95 96
		30	THF, 6 hr., reflux	96
$(C_6H_5)_2P=CFCl$	$C_6H_5CH=CHCl$ $(C_6H_5)_2C=CHCl$	46 20	THF, 6 hr., reflux $(C_6H_5)_2O$, -50; 3 days, 20	96 91.92
	$(C_6H_5)_2C=CFCl$	40	Heptane, 30 min., 40-50; 2 days, 20	94
$(C_6H_5)_2P=CCl_2$		33	Heptane, 30 min., 40-50; 2 days, 20	94
	$C_6H_5CH=CCl_2$	48	Heptane, 30 min., 40-50; 2 days, 20	94
	$2,6-Cl_2C_6H_3CH=CCl_2$	72	CCl_4 , 2 hr., 60	93
	$3,4-Cl_2C_6H_3CH=CCl_2$	46	Heptane, 30 min., 40-50; 2 days, 20	94
	$p-(CH_3)_2NC_6H_3CH=CCl_2$	43	Heptane, 30 min., 40-50; 2 days, 20	94
	$p-O_2NC_6H_3CH=CCl_2$	61	Heptane, 30 min., 40-50; 2 days, 20	94
	$C_6H_5CH=CHCH=CCl_2$	83	Heptane, 30 min., 40-50; 2 days, 20	94
	$n-C_{11}H_{23}CH=CCl_2$	77	Heptane, 30 min., 40-50; 2 days, 20	94
	$(C_6H_5)_2C=CCl_2$	29	Heptane, 30 min., 40-50; 2 days, 20	94
		69	Heptane, 30 min., 40-50; 2 days, 20	94
$(C_6H_5)_2P=CHBr$	$C_6H_5CH=CHBr$	48 78	Pentane/ $(C_6H_5)_2O$ CCl_4 , 4 hr., 60	93 95
$(C_6H_5)_2P=CHBr_2$	$C_6H_5CH=CHBr_2$	70	$(C_6H_5)_2O$	84
	$(C_6H_5)_2C=CHBr_2$	42	Heptane, 30 min., 40-50; 2 days, 20	94
		84	CH_2Cl_2	82
		0	Heptane, 30 min., 40-50; 2 days, 20	94

Note: References 391 to 404 are on p. 490.

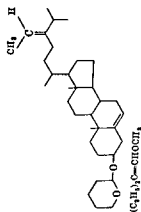
TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
$C_3 (C_4H_9)_3P=CHCH_3$	$CH_3O_2CC(CH_3)=CHCH_3$ $t-C_3H_7C(CH_3)=CHCH_3$	21	$(C_2H_5)_2O$, 12 hr., reflux $(C_2H_5)_2O$, 1 hr., 20; 3 hr., 65	164 306
			$(C_2H_5)_2O$, 46 hr., 20	174
			$(C_2H_5)_2O$, 7 days, 20	174
			$(C_2H_5)_2O$, 50 hr., 60	174
$(C_4H_9)_2C=CHCH_3$ $CH_3CO_2CH_2CH(CH_2)_8CH=CHCH_3$ $C_8H_4(C\equiv C)_3CH=CHCH_3$ $(C_4H_9)_3CCCH_2CH=CHCH_3$		98 67 5 58	$(CH_3)_2SO$, 3 hr., 25 $(C_2H_5)_2O$, 0 $(C_2H_5)_2O$, 1 hr., reflux $(C_2H_5)_2O$, 3 hr., 60	62 327 261 178
			$(C_2H_5)_2O$, 1 hr., 20; 15 hr., 65	378



$(C_2H_5)_2O$, 1 hr., 20; 5 hr., 65

307



$(C_2H_5)_2O$, 1 hr., 20; 16 hr., 65

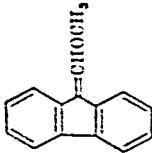
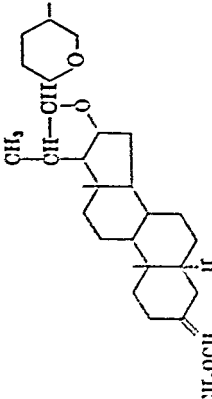
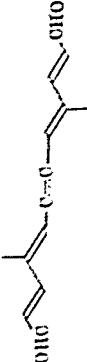
306

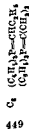
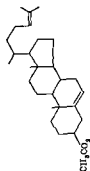
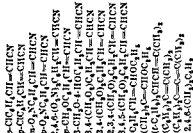
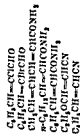
$(C_2H_5)_2P=CHOSi$

- 57 $(C_2H_5)_2O$, 5 hr., 20; 15 hr., 50 248
- 15 $(C_2H_5)_2O$, -40; 30 hr., 20 249
- 71 $(C_2H_5)_2O$, -30; 15 hr., 20 246, 248
- 40 $(C_2H_5)_2O$, 2 hr., 20 247
- 61 THF, 20 92
- 62 C_2H_5OH , 8 hr., 65 92
- 62 C_2H_5OH , 15 hr., 50 249

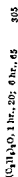
Note: References 391 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTING REACTION
A. Mono-glides as Starting Materials—Continued

Glide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
C_3 (C_2H_5) ₂ P—CHOCH ₃ (contd.)				
	$C_4H_9C(CH_3)=CHOCH_3$	40	(C_2H_5) ₂ O	246
	$C_4H_9CH=CHCH=CHOCH_3$	50	C_2H_5OH , 1 day, 50	92
	$n-C_4H_9C(CH_3)=CHOCH_3$	55	C_2H_5OH , 60 hr., 50	92
	$(C_2H_5)_2C=CHOCH_3$	83	(C_2H_5) ₂ O, 2 hr., 20	92, 247
				
		00	CH_3OH , 53 hr., 50	92
		85	(C_2H_5) ₂ O	246
	$C_4H_9CH=CHCH_3$	70	THF/(C_2H_5) ₂ O, 60 hr., 55	92
	$(C_4H_9)_2C=CHCH_3$	84	(C_2H_5) ₂ O, 40 hr., 20	92
	$n-C_4H_9CH=CHCHO$	81	C_6H_6 , 1 day, reflux	33,
	$C_4H_9CH=CHCHO$	00	C_6H_6 , 1 day, reflux	58 33, 58
		15	C_6H_6 , 10 hr., reflux	33, 58



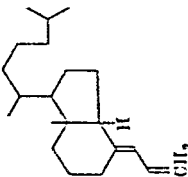
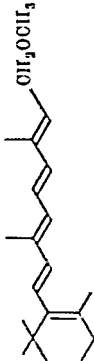
52	C_6H_5	20 hr., reflux	59
54	C_6H_5	20 hr., reflux	59
	C_6H_5OH		243
14	C_6H_5	20 hr., reflux	58
	C_6H_5	20 hr., reflux	59
	C_6H_5OH	2 days, 20	113
84	C_6H_5	4 hr., reflux	43, 58
73	C_6H_5	4 hr., reflux	43
76	C_6H_5	4 hr., reflux	43
72	C_6H_5	6-10 hr., 50-60	42
74	C_6H_5	6-10 hr., 50-60	42
71	C_6H_5	6-10 hr., 50-60	42
71	C_6H_5	4 hr., reflux	43
85	C_6H_5	4 hr., reflux	43
82	C_6H_5	4 hr., reflux	43
92	C_6H_5	4 hr., reflux	43
72	C_6H_5	4 hr., reflux	43
99	C_6H_5	4 hr., reflux	43
	$(C_6H_5)_2O$	12 hr., 20	113
	$(C_6H_5)_2O$	12 hr., 20	113
64	$(C_6H_5)_2O/TIP$	12 hr., 20	402
76	$(C_6H_5)_2O$	6 hr., 20	185
64	None	30 min., 145-160	150
50	None	30 min., 145-160	150
68	$(C_6H_5)_3O$		178

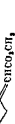
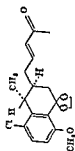


305

Note: References 391 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

Yldn	Product	Yield, %	Solvent, Time, Temperature, °C.	Refor- ences
C_8 (cont.) $(C_4H_9)_3P \cdots CHCH \cdots CH_3$	$HC \cdots CH \cdots CHCH \cdots CH_3$ $C_4H_9CH \cdots CHCH \cdots CH_3$ $C_4H_9N(CH_3)CH \cdots CHCH \cdots CH_3$ $CH_3CH \cdots CH(C \cdots O)_2CH \cdots CH_2CH \cdots CH_3$	58 20 50	$(C_2H_5)_2O$, 2 hr., 20 $(C_2H_5)_2O$, 2 hr., 20; 2 hr., 65 $(C_2H_5)_2O$, 2 hr., 20; 2 hr., 65 $(C_2H_5)_2O$, 2 hr., 20	179 2 255 250
			$(C_2H_5)_2O$, 2 days, 20	318
$(C_4H_9)_3P \cdots CHCH_2CH_2O$	$C_4H_9CH \cdots CHCH_2CH_2OH$	65	$(C_2H_5)_2O$	16
$(C_4H_9)_3P \cdots CHCH_2OCH_3$		10	$(C_2H_5)_2O$, 5-6 hr., reflux	281
$(C_4H_9)_3P \cdots C(CH_3)CHO$	$n-C_4H_9CH \cdots C(CH_3)CHO$	72	C_6H_6 , 1 day, reflux	33, 68
$(C_4H_9)_3P \cdots C(CH_3)CHO$	$C_4H_9CH \cdots C(CH_3)CHO$	60	C_6H_6 , 1 day, reflux	33, 68
$(C_4H_9)_3P \cdots CHCOCH_3$	$(CF_3)_3C \cdots CHCOCH_3$	93	C_2H_5O	210
$(C_4H_9)_3P \cdots CHCOCH_3$	$C_4H_9CH \cdots CHCOCH_3$	76	C_6H_6 , 3 days, reflux THF, 2 days, reflux	32 31
	$m-O_2NC_6H_4CH \cdots CHCOCH_3$	80	C_6H_6 , 6-10 hr., 50-60	42
	$p-O_2NC_6H_4CH \cdots CHCOCH_3$	92	C_6H_6 , 6-10 hr., 50-60	42
	$2,4,6-(O_2N)_3C_6H_2CH \cdots CHCOCH_3$	78	C_6H_6 , 6-10 hr., 50-60	42



THF, 30 hr., reflux

404

93

None, 30 hr., 90-95

48

C_6H_6 , 35 hr., reflux

59

C_6H_6 , 8 hr., reflux

83

None, 90 min., 80-90

30

None, 150

36

C_6H_6 , 4 hr., reflux

C_6H_6 , 10 hr., reflux

C_6H_6 , 10 hr., reflux

C_6H_6 , 10 hr., reflux

C_6H_6 , 10 hr., reflux

93

CH_2Cl_2 , 8 hr., 20

95

C_6H_6 , 10 hr., reflux

C_6H_6 , 8 hr., reflux

85

CH_2Cl_2 , 12 hr., 20

60

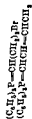
C_6H_6 , 1 day, reflux

237

Note References 391 to 404 are on p. 490

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

Ylide $C_3-C_4H_5P-CHCO_2CH_3$ (contd.)	Product	Yield, %	Solvent, Time, Temperature, °C.	References
		58	Xylene, reflux None, 160	30 36
			CH_2Cl_2 , 5 hr., reflux	298
		80	CH_2Cl_2 , 5 hr., reflux C_6H_6 , 0 hr., reflux	231 39
			CH_2Cl_2 , 5 hr., reflux	231
			CH_2Cl_2 , 5 hr., reflux	295- 297
			CH_2Cl_2 , 5 hr., reflux	295- 297



Note: References 391 to 404 are on p. 490.

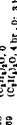
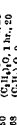
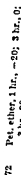
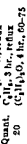
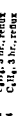
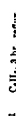
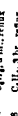
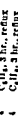
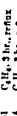
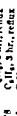
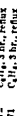
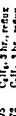
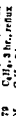
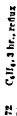
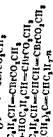
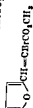
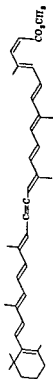



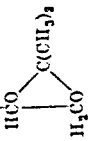


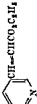

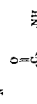


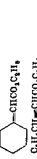








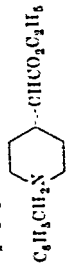
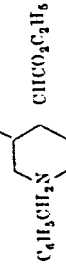
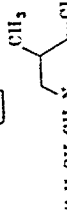
TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-glides as Starting Materials—Continued

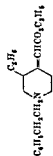
Yield	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
$(C_2H_5)_3P-CHC(CH_3)=CH_2$	$i-C_4H_9CH=CHC(CH_3)=CH_2$		THF, 4 hr., reflux	394
			THF, 4 hr., reflux	394
$(C_2H_5)_3P-CHCOC_2H_5$	$CCl_3-CClCH=CHCOC_2H_5$	53	C_6H_6 , 8 hr., reflux	59
$(C_2H_5)_3P-CHCOC_2H_5$	$CCl_3-CClCH=CHCOC_2H_5$	87	C_6H_6 , 8 hr., reflux	59
$(C_2H_5)_3P-CHCOC_2H_5$	$C_2H_5CH=CHCOC_2H_5$	49	C_6H_6 , 6 hr., reflux	220
$(C_2H_5)_3P-CHCOC_2H_5$	$(CH_3)_2C=CHCOC_2H_5$	45	None, 1 day, 100	35
	$CH_2FC(CH_3)=CHCOC_2H_5$	65	C_6H_6 , 6 hr., reflux	218
	$CH_3CHBrCH=CHCOC_2H_5$	34	C_6H_6 , 6 hr., reflux	220
	$CH_3-CH=CH-CHCOC_2H_5$	42	None, 1 day, 100	35
	$C_2H_5C(CH_3)=CHCOC_2H_5$	80	C_6H_6 , 6 hr., reflux	220
	$C_2H_5CH=CHCO_2C_2H_5$	50	C_6H_6 , 6 hr., reflux	220
	$C_2H_5OCH_2CH_2CH=CHCOC_2H_5$			
		43	None, 10 hr., 170	35
		51	C_6H_6 , 6 hr., reflux	220
	$CHCO_2C_2H_5$ \parallel CH	75		238
				
	$CH_3CH=CHCO_2C_2H_5$	87	C_6H_6 , 6 hr., reflux	220

	23	C ₈ H ₁₀ or C ₈ H ₈ CH ₂ , reflux	37
	45	C ₂ H ₅ OH, 7 days, 20	34
	60	None, 10 hr., 170	35
	98	C ₂ H ₅ OH, 3-15 days, 20	34
	91	C ₂ H ₅ OH, 3-15 days, 20	34
	89	C ₂ H ₅ OH, 3-15 days, 20	34
	30	Dioxane, 7 hr., reflux; 12 hr., 20	221
	70	C ₆ H ₆ , reflux	239
	7	C ₂ H ₅ OH, 12 days, 20	34
	77	C ₂ H ₅ OH, 2 days, 20	3
	Quant.	C ₆ H ₆ , 6 hr., reflux	220
	71	C ₂ H ₅ OH, 3-15 days, 20	34
	89	C ₂ H ₅ OH, 3-15 days, 20	34

Note: References 391 to 404 are on p. 490.

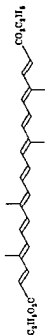
TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. *Mono-ylides as Starting Materials—Continued*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
$C_4(C_2H_5)_3P \cdots CHCO_2C_2H_5$ (contd.)	$C(CH_3) \cdots CHCO_2C_2H_5$	90	C_2H_5OH , 3–15 days, 20	34
				
	$CH_3(CH \cdots CH)_2CO_2C_2H_5$	92	C_6H_6 , 6 hr., reflux	220
	C_2H_5	0	C_2H_5OH , 12 days, 20	34
		58	None, 10 hr., 170	35
	$C(CH_3) \cdots CHCO_2C_2H_5$	05		230
	$C_6H_5(C(CH_3) \cdots CHCO_2C_2H_5)$	71	C_6H_6 , 6 hr., reflux	220
	$CH_3C(CH_3)C \cdots CH \cdots C(CH_3)CH \cdots CHCO_2C_2H_5$	88	C_6H_6 , 6 hr., reflux	220
	$C_6H_5CH \cdots CHCH \cdots CHCO_2C_2H_5$	68	C_6H_6 , 6 hr., reflux	217
	$(CH_3)_2C \cdots CH(CH_2)_2C(CH_3) \cdots CHCH \cdots CHCO_2C_2H_5$	Quant.	C_6H_6 , 6 hr., reflux	327
	$C_6H_5O_2CCH \cdots C(CH_3)CH \cdots CHCO_2C_2H_5$		C_6H_6 , 6 hr., reflux	163
	$C_2H_5O_2C(CH \cdots CH)_2CO_2C_2H_5$	80	C_2H_5OH , 3–15 days, 20	34
		54	None, 10 hr., 170	35
	$(C_4H_9)_3C \cdots CHCO_2C_2H_5$			
				
	$C_6H_5CH_2N \cdots CHCO_2C_2H_5$	21	C_2H_5OH , 3–15 days, 20	34
				
	$C_4H_9CH_2CH_2N \cdots CHCO_2C_2H_5$	10	C_2H_5OH , 3–15 days, 20	34



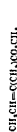
20 $\text{C}_2\text{H}_5\text{OH}$, 3-15 days, 20

34



CH_2Cl_2 , 5 hr., reflux

39



90 CH_2Cl_2 , 12 hr., 20

164

60 CH_2Cl_2 , 3.5 hr., reflux

164

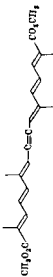


C_6H_6 , 6 hr., reflux

39

CH_2Cl_2 , 5 hr., reflux

231



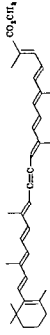
CH_2Cl_2 , 5 hr., reflux

231



CH_2Cl_2 , 6 hr., reflux

205-207



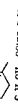
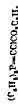
CH_2Cl_2 , 6 hr., reflux

205-207



CH_2Cl_2 , 6 hr., reflux

205-207

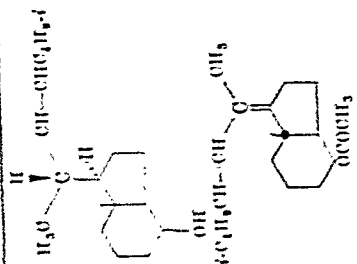
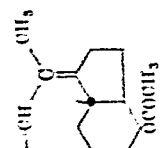
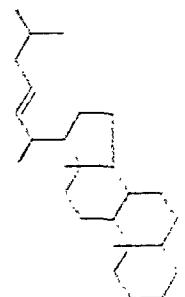
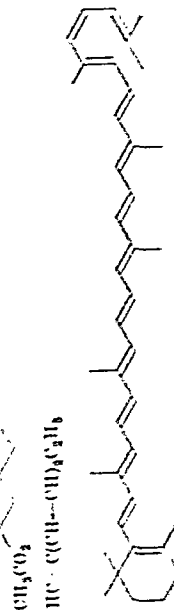
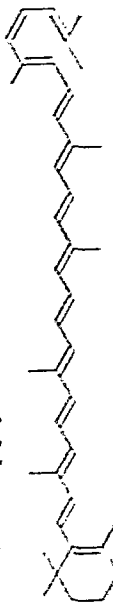


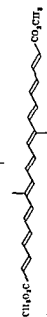
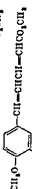
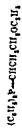
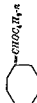
None, 12 hr.

60

Note: References 301 to 404 are on p. 460.

TABLE VI—Continued
OLDFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

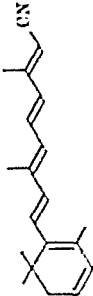
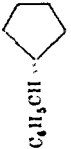
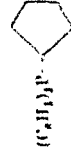

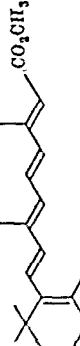
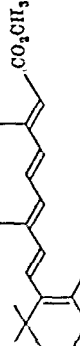
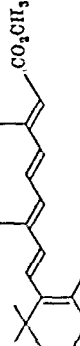
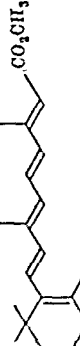
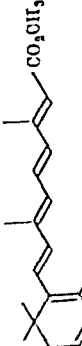
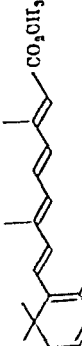
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ence
$C_6H_5CH_2P(=CHC_6H_5)_2$		40	Dioxane, 12 hr., 110	321
			Dioxane, 11 hr., 100	320
			$(C_2H_5)_2O$, 1 hr., 20; 15 hr., 05	378
$(C_6H_5)_2P(=CHCH=CHC_6H_5)_2$			$(C_2H_5)_2O$, 30 min., 80	200
$(C_6H_5)_2P(=CHCH=CHC(CH_3)_2)_2$			CH_2Cl_2 , 20 hr., 20	205




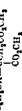


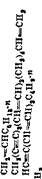
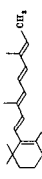
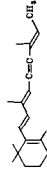
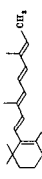
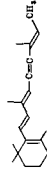
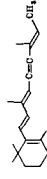
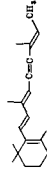


73	$(C_4H_9)_3C-CHOC_4H_9$	$(C_4H_9)_2O$, -40; 4 hr., 20	248
40	$(C_4H_9)_3C-CHOC_4H_9$	$(C_4H_9)_2O$, -30; 18 hr., 20	248
74	$(C_4H_9)_3C-CHOC_4H_9$	$(C_4H_9)_2O$, -30; 18 hr., 20	248
46	C_2H_5OH , 7 hr., -30; 16 hr., 20	C_2H_5OH , 7 hr., -30; 16 hr., 20	248
35	$(C_4H_9)_3C-CHOC_4H_9$	$(C_4H_9)_2O$, -30; 18 hr., 20	248
39	C_4H_9 , -10; 15 hr., 20	C_4H_9 , -10; 15 hr., 20	248
66	$(C_2H_5)_2O$	$(C_2H_5)_2O$	138
	CH_3CH_2 , 5 hr., reflux	CH_3CH_2 , 5 hr., reflux	39
33	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
25	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
3	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
40	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
48	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
25	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
46	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
50	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
35	CH_3OH , 15 min., 20	CH_3OH , 15 min., 20	242
79	C_4H_9 , 6 hr., reflux	C_4H_9 , 6 hr., reflux	232, 235
79	C_4H_9 , 6 hr., reflux	C_4H_9 , 6 hr., reflux	234

See References 231 to 404 and p 490.

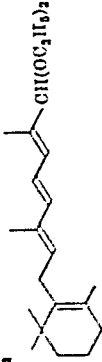
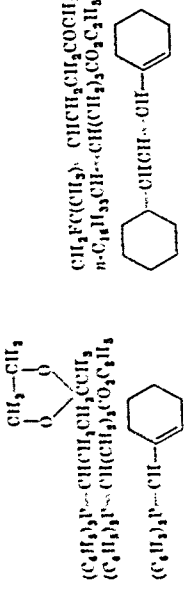
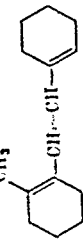

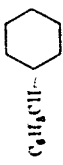




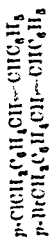
TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-glides as Starting Materials—Continued

Yld.	Product	Yield, %	Solvent, Time, Temperature, °C.	References
$C_3(c-c)$ $(C_4H_9)_3P-CH(C_2H_5)-CHCN$		86	CH_3CN , 1 hr., 20; 2.5 hr., 80	244
C_4 $(C_4H_9)_3P-CH(C_2H_5)-CHCN$		65	$(C_2H_5)_2O$, 10 hr., 30	185
C_5 $(C_4H_9)_3P-CH(C_2H_5)-CHCN$		65	$(C_2H_5)_2O$, 0	327
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$	68	$(C_2H_5)_2O$, 2 hr., 0; 1 hr., 20	161
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$	75	Pet. ether, 3-12 hr., 0	326
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$	70	Pet. ether, 2 hr., 0; 1 hr., 20	161, 326
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$	15	C_2H_5OH , 4 hr., reflux	325
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$	12	$(C_2H_5)_2O$, 4 hr., 60-75	182
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$	47	C_2H_5OH , 1 day, reflux	325
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$	76	$(C_2H_5)_2O$, 0	328
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$		$(C_2H_5)_2O/THF$, 30 min., 20	181
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$		$(C_2H_5)_2O/THF$, 15 min., 20	181
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$	$CH_3CO_2CH_2CH_2CH=CHCH=CHC_2H_5$		$(C_2H_5)_2O$, 2 hr., reflux	376, 377
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$		10	C_4H_6 , 6 hr., 60	280a
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$			C_6H_6 , 5 hr., reflux; 12 hr., 20	163
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$			C_2H_5OH , 2 hr., 20	282
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$			C_6H_6 , 2 hr., 20; 30 min., 60	55
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$			DMF, 2 hr., 20	55
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$		87	CH_3CN , 1 hr., 20; 3 hr., 85	244
$(C_4H_9)_3P-CH(C_2H_5)-CHCN$		90	Tetramethylene sulfone, 1 hr., 20; 2 hr., 80	244

$(C_6H_5)_3P=CHCH=C(CH_3)CO_2CH_3$	$C_6H_5(CH=CH)_3CH=C(CH_3)CO_2CH_3$	C_6H_5 , 6 hr., reflux	232, 235
$(C_6H_5)_3P=CHCH=C(CH_3)CO_2CH_3$		C_6H_5 , 6 hr., reflux	232, 235
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		CH_3Cl , 6 hr., reflux	297
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		C_6H_5 , 6 hr., reflux	233, 234
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		C_6H_5 , 12 hr., reflux	40
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		$(C_2H_5)_2O$, 1 day, 20; 3 hr., reflux	113
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		$(C_2H_5)_2O$, 12 hr., 20; 8 hr., 50	185
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		$(C_2H_5)_2O$, 10-12 hr., 20	189, 189
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		$(C_2H_5)_2O$, 2 hr., reflux	180
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		$(C_2H_5)_2O$, 1 hr., 0	259
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		$(C_2H_5)_2O$, 2 hr., 20	287
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		C_6H_5 , 20 hr., 20	287
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		DMF, 16 hr., 20	287
$(C_6H_5)_3P=CHCH=CHCO_2CH_3$		THF, 16 hr., 20	209

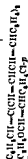
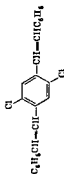
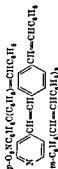
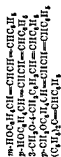
Note: References 291 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
$C_4(COOEt)_2$ $(C_2H_5)_2P-CHCH-COC_2H_5$		79	CH_3OH , 16 min., 55; 8 hr., 00	216
$(C_2H_5)_2P-CHCH-COC_2H_5$ $(C_2H_5)_2P-CHCH-COC_2H_5$ $(C_2H_5)_2P-CHCH-COC_2H_5$		50	DMF $(C_2H_5)_2O$, 3 hr., 05	218 114 168
$(C_2H_5)_2P-CHCH-COC_2H_5$		80	$(C_2H_5)_2O$, 1 hr., 20; 3 hr., 05	314
$(C_2H_5)_2P-CHCH-COC_2H_5$		04-75	$(C_2H_5)_2O$ DMF, 5 hr., 00	188, 189 113
$(C_2H_5)_2P-CHCH-COC_2H_5$		00	$(C_2H_5)_2O$, 4 hr., 20; 1 day, 70	3
$(C_2H_5)_2P-CHCH-COC_2H_5$		82	$(C_2H_5)_2O$, 2 days, 20	2
$(C_2H_5)_2P-CHCH-COC_2H_5$		28	TUHF, 2 hr., reflux	90
$(C_2H_5)_2P-CHCH-COC_2H_5$		78	C_2H_5OH , 1 day, 20	3
$(C_2H_5)_2P-CHCH-COC_2H_5$		70-75	C_2H_5OH , 1 hr., 20	100
$(C_2H_5)_2P-CHCH-COC_2H_5$			C_2H_5OH , 1 hr., 20	100



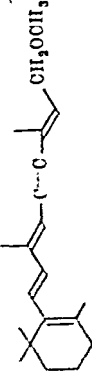



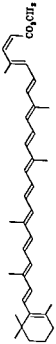

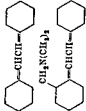
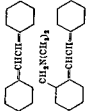
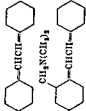
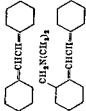
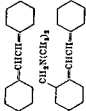
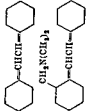
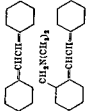
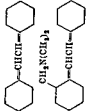
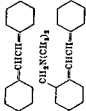
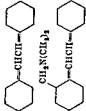
78	$(C_2H_5)_2O$, 3 hr., reflux THF, 12 hr., 20	209
	THF, 1 hr., 60	209
84	C_2H_5OH , 30 min., 20	65
31	C_2H_5OH , 3 days, 20	66
43	C_2H_5OH , 3 days, 20	66
56	$(C_2H_5)_2O$, 30 min., reflux	194
67	C_2H_5OH , 8 hr., 50	66
46	$(C_2H_5)_2O$, 2 days, 75	3
23	THF, 5 hr., reflux	90
76	$(C_2H_5)_2O$, 1 hr., 20	3
47	$(C_2H_5)_2O$, 10 hr., 75	3
52	C_2H_5OH , 2 hr., 20	108
27	C_2H_5OH , 1 day, 20	66
	DMF	201
	$(C_2H_5)_2O/THF$, 1 hr., 20	213
	$(C_2H_5)_2O/THF$, 1 hr., 20	218
	THF, 5 hr., 20	209
	$(C_2H_5)_2O/THF$, 1 hr., 20	213
	C_2H_5 , 2 days, 20	113



Note: References 391 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-glides as Starting Materials—Continued

Yield	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_7 (contd.) $(C_2H_5)_3P-CHC_6H_5Cl_2-2,4$	$p-C_6H_4 \left(CH-CH \left(\begin{array}{c} Cl \\ \\ \text{C}_6H_4Cl \end{array} \right) \right)_2$	DMF		201
$(C_2H_5)_3P-CHC_6H_5NO_2-m$	$C_6H_5CH-CHCH-CHC_6H_5NO_2-m$	05	C_6H_5OH , 20	210
$(C_2H_5)_3P-CHC_6H_5NO_2-p$	$p-CH_3OC_6H_4CH-CH-CHC_6H_5NO_2-p$	80	C_6H_6 , 4 hr., 20	100
	$m-C_6H_4 \left(CH-CH \left(\begin{array}{c} NO_2 \\ \\ \text{C}_6H_4NO_2 \end{array} \right) \right)_2$	51	C_2H_5OH , 2 hr., 40	60
$(C_2H_5)_3P-CHOC_6H_5$		68	$(C_2H_5)_2O$, 20	248
	$C_6H_5CH-CHOC_6H_5$	56	$(C_2H_5)_2O$, 20	248
	$(C_2H_5)_2C-CHOC_6H_5$	65	$(C_2H_5)_2O$, 20	248
C_8 	$CH_3(C-C_6H_4-CH_2CH_2OH$		$(C_2H_5)_2O$, 3 hr., reflux	71
	$(C_2H_5)_3P-CHC-CC(C_6H_5)-CHCH_2OCH_3$			
		10	$(C_2H_5)_2O$, 10 min., 20	200
$(C_2H_5)_3P-CC(C_6H_5)COC_6H_5-m$	$C_6H_5CH-CC(C_6H_5)COC_6H_5-m$	40	C_6H_6 , 1 day, reflux	32
$(C_2H_5)_3P-CHCH-CC(C_6H_5)CH-CHCO_2CH_3$			CH_2Cl_2 ; 1 hr., 20; 5 hr., reflux	230

	CH_3Cl , 6 hr., reflux	297
	CH_3Cl , 6 hr., reflux	297
	THF, 2 hr., reflux	183, 184
	$(\text{C}_2\text{H}_5)_2\text{O}$ 1 day, 20	183, 184
	$(\text{C}_2\text{H}_5)_2\text{O}$, 1 hr., 20, 3 hr., 65	158
	THF, -65; 18 hr., 20	69
	$\text{C}_2\text{H}_5\text{OH}$, 3 hr., 20; 15 min., 70	66
	$\text{C}_2\text{H}_5\text{OH}$, 2 hr., 80	66
	$\text{C}_2\text{H}_5\text{OH}$, 2 hr., 20	195
	$\text{C}_2\text{H}_5\text{OH}$, 30 min., 20	196
	THF, 1 day, 20	113
	C_2H_5 , 4 hr., 20	166

Note: References 291 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTING REACTION
A. Mono-ylides as Starting Materials—Continued





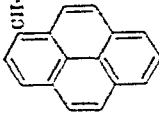
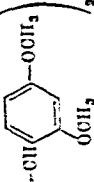
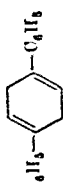
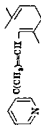
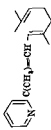
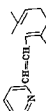
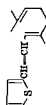
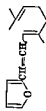
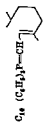
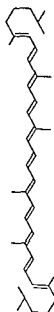
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
C_4 (cond.) $(C_4H_9)_3P=CHC_6H_5(O_2CH_3)_3$.4	$p-C_6H_4 \left(CH=CH \begin{array}{c} O \\ \diagup \quad \diagdown \\ CH_3 \quad O \end{array} \right)_2$	72	DMF	201
$(C_4H_9)_3P=CHOC_6H_4CH_3$.p	$(C_6H_5)_2C=CHOC_6H_4CH_3$.p	82	$(C_2H_5)_2O$, 20	248
		58	$i-C_4H_9OH$, 8 hr., 65	248
	$C_6H_5CH=CHOC_6H_4CH_3$.p	75	$(C_2H_5)_2O$, 20	248
	$(C_4H_9)_2C=CHOC_6H_4CH_3$.p	64	$i-C_4H_9OH$, 8 hr., 65	248
		67	$(C_2H_5)_2O$, 20	248
		61	$i-C_4H_9OH$, 8 hr., 65	248
	$CH=CHC(CH_3)=CHOC_6H_4CH_3$.p	73	$(C_2H_5)_2O$, 2 hr., 20	248
		75	$(C_2H_5)_2O$, 2 hr., 20	248
	$o-C_6H_4 \left(CH=CHO \begin{array}{c} CH_3 \\ \\ \text{benzene ring} \end{array} \right)_2$	62	$(C_2H_5)_2O$, 20	248
$(C_4H_9)_3P=CHCOC_6H_5$	$C_6H_5CH=CHCOC_6H_5$	70	C_6H_6 , 3 days, reflux	32
$(C_4H_9)_3P=CClCOC_6H_5$	$C_6H_5CH=CClCOC_6H_5$	Quant.	THF, 30 hr., reflux	31
$(C_4H_9)_3P=CHCOC_6H_5$	$p-O_2NC_6H_4CH=CClCOC_6H_5$	64	None, 2 days, 100	60
$(C_4H_9)_3P=CHCOC_6H_5$	$p-O_2NC_6H_4CH=CHCOC_6H_5$	60	C_6H_6 , 35 hr., reflux	59
		60	C_6H_6 , 36 hr., reflux	59

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
C_9 (anti-1) $(C_2H_5)_3P=CHCH=CHC_6H_5$		62	C_2H_5OH , 2 hr., 20	211
	$C_6H_5CH=CHCH_2C(C_6H_5)=CHCH=CHC_6H_5$ $(C_2H_5CH=CHCH_2C=CHCH=CHC_6H_5)$ $C_2H_5CH=CHCH=CH_2C=CHCH=CHC_6H_5$ $(C_2H_5CH=CHCH=CHCH_2C=CHCH=CHC_6H_5)$		THF, 15 min., 20; 45 min., reflux $(C_2H_5)_2O/THF$, 1 hr., 20 $(C_2H_5)_2O/THF$, 1 hr., 20 $(C_2H_5)_2O/THF$, 1 hr., 20	213 213 213 213
	$p-C_6H_4\left(CH=CH\begin{array}{c} \text{OCH}_3 \\ \text{OCH}_3 \end{array}\right)_2$		DMF	201
$(C_2H_5)_3P=CHC_6H_4(OC_2H_5)_2$, 2,4		12	C_2H_5OH , 30 hr., reflux	203
$(C_2H_5)_3P=CHCH_2COC_6H_5$		38	C_2H_5OH , 20	210
$(C_2H_5)_3P=CHC_6H_4CO_2CH_3$, p	$C_6H_5CH=CHCH=CHC_6H_4CO_2CH_3$, p $p-C_6H_4\left(CH=CH\begin{array}{c} \text{CO}_2CH_3 \\ \text{CO}_2CH_3 \end{array}\right)_2$	73	C_2H_5OH , 30 min., 20 DMF or $(CH_3)_2SO$	103 109, 200
$(C_2H_5)_3P=CHC_6H_4N(C_2H_5)_2$, p	$C_6H_5CH=CHCH=CHC_6H_4N(C_2H_5)_2$, p	60	C_2H_5OH , 20	210



CH_3Cl , 5 hr., reflux
276,
277

81 $(C_4H_7)_3O$, 3-4 hr., reflux 397

72 $(C_4H_7)_2O$, 3-4 hr., reflux 397

63 $(C_4H_7)_2O$, 3-4 hr., reflux 397

68 $(C_4H_7)_2O$, 3-4 hr., reflux 397

61 $(C_4H_7)_2O$, 3-4 hr., reflux 397

48 $(C_4H_7)_2O$, 3-4 hr., reflux 397

60 $(C_4H_7)_2O$, 3-4 hr., reflux 397

Note: References 391 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
C_4 , $(C_4H_9)_3P=CH-$ 	(contd.) 	53	$(C_2H_5)_2O$, 3-4 hr., reflux	397
		62	$(C_3H_7)_2O$, 3-4 hr., reflux	397
		59	$(C_2H_5)_2O$, 3-4 hr., reflux	397
		43	$(C_2H_5)_2O$, 3-4 hr., reflux	397
		75	$(C_2H_5)_2O$, 3-4 hr., reflux	397
		53	$(C_2H_5)_2O$, 5 hr., 0; 6-7 hr., 20	328
		70	CH_2Cl_2 , 15 min., 30; 5 hr., reflux DMF, 2 hr., 20	275, 276 274

	$(C_6H_5)_3P=CH-$		CH_2Cl_2 , 15 min., 30; 5 hr., reflux DMF, 2 hr., 20	275, 276 274
			CH_2Cl_2 , 5 hr., reflux	264
			CH_3OH	270
			CH_3OH	279
			$(C_2H_5)_2O$, 2 hr., reflux	241
			$(C_2H_5)_2O$, 2 days 0 DMF	259 114
			DMF, 5 hr., 60	113
			$(C_2H_5)_2O$, 2 hr., reflux DMF, 6 hr., 20	293 293
			DMF/ $(C_2H_5)_2O$, 2 hr., 20	293

Note: References 291 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
$C_{10}(C_4H_9)_2P-CH-$ 		53	$(C_2H_5)_2O$, 3 hr., 0; 6 hr., 20; 1 hr., reflux	328
(contd.)		68	$(C_2H_5)_2O$, 0	328
			THF, 1 hr., 00	209
			THF, 1 hr., 00	209
		3	CH_2Cl_2 , 15 min., 30; 5 hr., reflux; DMF, 1 hr., 20	273 274
		3	C_6H_6 , 0 hr., 00 $(C_2H_5)_2O/C_6H_6$, 1 hr., 40	273 275
$(C_4H_9)_2P-C(CH_2C_4H_9)CO_2CH_3$		42	C_6H_6 , 10 hr., reflux	40

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

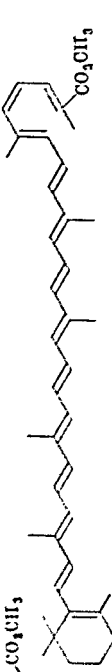
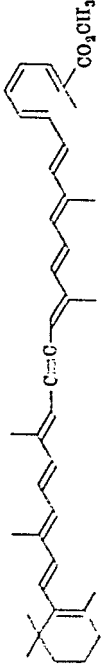
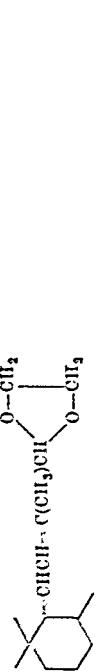





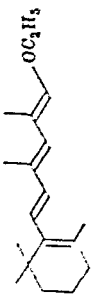
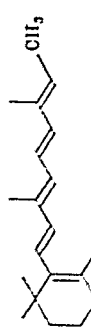
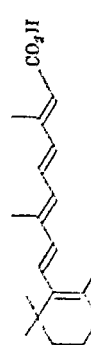
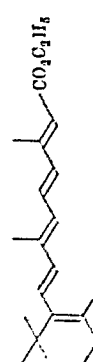
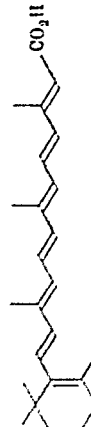
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
$C_{11} (C_6H_5)_3P-CH=C(CH_3)-CH=CH-CO_2CH_3$			CH_2Cl_2 , 6 hr., reflux	207
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$			CH_2Cl_2 , 6 hr., reflux	207
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$			$(C_6H_5)_2O/C_6H_6$, 20 min., 20; 0 hr., 60	214
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$		26	C_6H_5OH , 23 hr., 20	107
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$		38	C_6H_5OH , 23 hr., 20	107
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$		61	C_6H_5OH , 23 hr., 20	107
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$		24	C_6H_5OH , 30 min., reflux	202
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$		64	C_6H_6 , 3 days, reflux	32
$(C_6H_5)_3P-CH=CH-C(CH_3)_2-CH=CH-CO_2CH_3$		81	C_6H_6 , 4 days, reflux	32

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-ylides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
$C_{11} (C_4H_9)_3P=C(CH_3)CH=CH-$ (cont'd)			$(C_2H_5)_2O$, 2 hr., 20; 6 hr., reflux	240
			DMF, 2 hr., 20	240
		70	C_6H_6 , 1 hr., 20 DMF, 2 hr., 20	240 289
		80	DMF, 30 min., 20 DMF, -40; 5 min., -10	291 292
		70	DMF, 2 hr., 20 DMF, 1 hr., 70 DMF, -40; 5 min., -10	289 289 292
			DMF, 15 min., 20	240



THF, 2 hr., 60

209



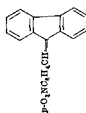
DMF, 1 hr., 20

240,
272



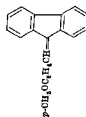
49

84 CHCl₃, 3 hr., reflux



49

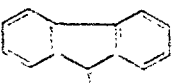
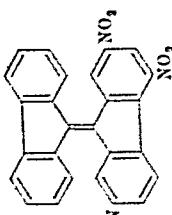

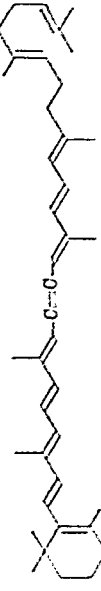

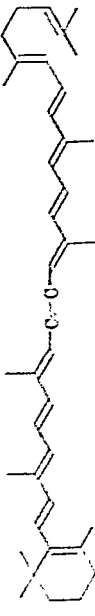
98 CHCl₃, 3 hr., reflux

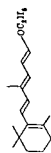


49

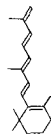
37 CHCl₃, 3 hr., reflux

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-olides as Starting Materials—Continued

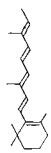
Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
C_{10} $(C_6H_5)_3P^{+} \cdots (cont. Li)$ 		Quant.	$CHCl_3$, 3 hr., reflux	49
C_{10} $(C_6H_5)_3P^{+} \cdots C(C_6H_5)_2CH_2CH_2C_6H_5$ C_{10} $(C_6H_5)_3P^{+} \cdots C(C_6H_5)_2$	$C_6H_5CH_2 \cdots C(C_6H_5)_2CH_2CH_2C_6H_5$ $(C_6H_5)_2C \cdots C \cdots C(C_6H_5)_2$	80 46	C_6H_6 , 3 days, reflux TME, 12 hr., reflux	32 123
C_{10} $(C_6H_5)_3P^{+} \cdots CHCH \cdots C(CH_3)CH_2CH_3$ 			DMF, 12 hr., 0	205
C_{10} $(C_6H_5)_3P^{+} \cdots CHCH \cdots C(CH_3)CH \cdots CH$ 			DMF, 10 hr., 20	204



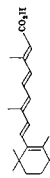
DMF, 12 hr., 20
269,
270



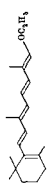
DMF, 3 hr., 20
269,
270



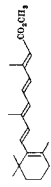
20 DMF, 8 hr., 20
DMF, 2 hr., 20
C2H5OH, 1 hr., -15;
12 hr., 20
287
270,
284
285



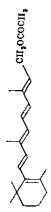
DMF, 4 hr., 0
CH3OH, 1 hr., 20
C2H5OH, 1 hr., -15;
12 hr., 20
284
270,
286
285



CH3OH/C2H5, 5 hr., 20
CH3OH, 10 hr., 20
289
270



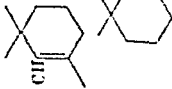
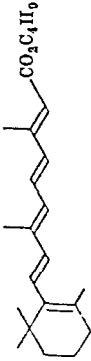
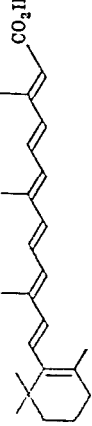
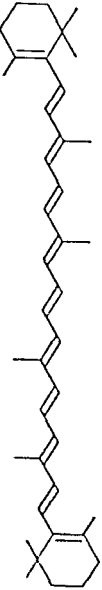
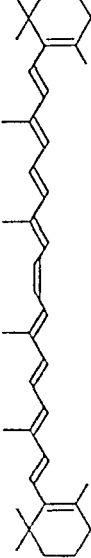

None, 3 hr., 5
CH3OH, -20; 5 hr., 0
285
286

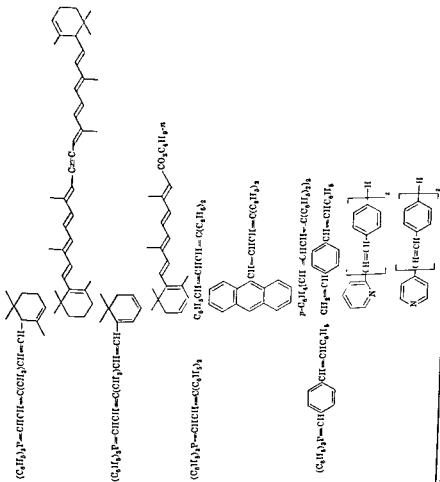


DMF, 5 hr., 0
CH3OH, 2 hr., -10; 12 hr., 20
270,
284
285

Note. References 301 to 404 are on p. 490.

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
A. Mono-glides as Starting Materials—Continued

Yld.	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
C_{15} (C_8H_{15}) ₂ P-, CHCH- $C(CH_3)CH=CH$ (cont.)		70	(C_2H_5) ₂ O THF, 30 min., -30; 18 hr., 20 C_6H_6 DMF, 30 min., -10; 2 hr., 20 DMF, 6 hr., 20 CH_3OH , 1 hr., 20 CH_3OH , 45 min., -30; 4 hr., 20 C_2H_5OH , 30 min., -10; 2 hr., 20	283 285 283 284 283 284 285 285
			DMF, 10 hr., 20	270
			DMF, 15 min., 20 CH_3OH , 15 min., 20 C_2H_5OH , 1 hr., 20	269, 294 270 294
			(C_2H_5) ₂ O or C_6H_6 , 10 hr., 20 DMF, 1-3 hr., 20	54 208- 270
			C_2H_5OH /DMF, 3 hr., 20	208
			DMF, 1-2 hr., 20 DMF, 20 hr., 20 C_2H_5OH , 2 hr., 20; 10 min., reflux	268, 270 264 54



Note. References 391 to 404 are on p 490

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTING REACTION
A. Mono-olides as Starting Materials—Continued

Ylide	Product	Yield, %	Solvent, Temp., °C.	References
C_{11} $(C_6H_5)_3P \sim CH \sim \text{C}_6H_5 \sim CH=CHC_6H_5$ (<i>conf. I</i>)	 $p\text{-BrCH}_2C_6H_4CH=CHC_6H_5$ $C_6H_5C \equiv C \text{C}_6H_4CH=CHC_6H_5$ $C_6H_5CH=CHC_6H_4CH=CHC_6H_5$ $C_6H_5CH=CHC_6H_4CH=CHC_6H_5$	45	C_2H_5OH , 2 hr., 20	108
C_{12} $(C_6H_5)_3P \sim CH \sim \text{C}_6H_5 \sim CH=CHC_6H_5$	 $p\text{-BrCH}_2C_6H_4CH=CHC_6H_5$ $C_6H_5C \equiv C \text{C}_6H_4CH=CHC_6H_5$ $C_6H_5CH=CHC_6H_4CH=CHC_6H_5$	63-65	C_2H_5OH , 1 hr., 20	100
C_{13} $(C_6H_5)_3P \sim CH \sim \text{C}_6H_5 \sim CH=CHC_6H_5$	 $p\text{-BrCH}_2C_6H_4CH=CHC_6H_5$ $C_6H_5C \equiv C \text{C}_6H_4CH=CHC_6H_5$ $C_6H_5CH=CHC_6H_4CH=CHC_6H_5$	38-40	C_2H_5OH , 2 hr., 20	211
C_{14} $(C_6H_5)_3P \sim CH \sim \text{C}_6H_5 \sim CH=CHC_6H_5$	 $p\text{-BrCH}_2C_6H_4CH=CHC_6H_5$ $C_6H_5C \equiv C \text{C}_6H_4CH=CHC_6H_5$ $C_6H_5CH=CHC_6H_4CH=CHC_6H_5$	57	C_2H_5OH	106
C_{15} $(C_6H_5)_3P \sim CH \sim \text{C}_6H_5 \sim CH=CHC_6H_5$	 $p\text{-BrCH}_2C_6H_4CH=CHC_6H_5$ $C_6H_5C \equiv C \text{C}_6H_4CH=CHC_6H_5$ $C_6H_5CH=CHC_6H_4CH=CHC_6H_5$	91	C_2H_5OH	107
C_{16} $(C_6H_5)_3P \sim CH \sim \text{C}_6H_5 \sim CH=CHC_6H_5$	 $p\text{-BrCH}_2C_6H_4CH=CHC_6H_5$ $C_6H_5C \equiv C \text{C}_6H_4CH=CHC_6H_5$ $C_6H_5CH=CHC_6H_4CH=CHC_6H_5$		PI_2Cl_2 , 5 hr., reflux	39

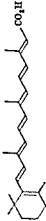


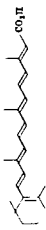
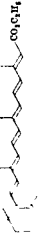


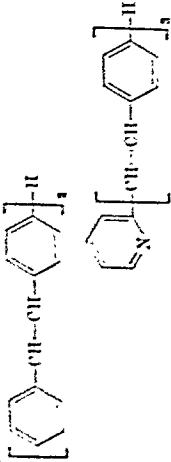

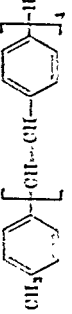
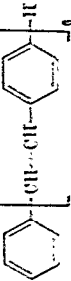
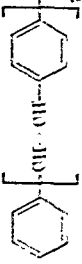
$(C_2H_5)_3P-$		DMF, 1 hr., 20	270
$C_{18} (C_2H_5)_3P-C(CH_3)_2CO_2C_{10}H_{21}-n$		CH_2Cl_2 , 5 hr., reflux	39
$C_{30} (C_2H_5)_3P-$		$(C_2H_5)_2O$, 3 hr., 20	267
$(C_2H_5)_3P-$		DMF, 15 min., 20	268
$(C_2H_5)_3P-$		DMF, 3 hr., 0; 1 hr., 20	266
$(C_2H_5)_3P-$		CH_3OH , 15 hr., 20	265
$(C_2H_5)_3P-$		C_4H_9OH , 2 hr., 20	264

TABLE VI—Continued
 OFFERINS PREPARED BY THE WITTIG REACTION
 A. Mono-phides as Starting Materials—Continued

Yldo	Product	Yield, %	Solvent, Time, Temperature, °C.	Refer- ences
C_4 $(C_4H_5)_3P-CH-[C_6H_4-CH-CH-]_3-H$		50	C_2H_5OH , 2 hr., 20	108
			C_2H_5OH , 2 hr., 20	108
			C_2H_5OH , 2 hr., 40	100
		42	C_2H_5OH , 2 hr., 40	100
		32	C_2H_5OH , 2 hr., 40	100

B. Bis-phides as Starting Materials



C_4 $(C_4H_5)_3P-CHOCN-PC_4H_5)_2$

CH_3OH

100



C_2	$(C_2H_5)_2P-CHCH_2CH-PC_2H_5$		$C_2H_5CH=CHCH_2CH=CHC_2H_5$	$(C_2H_5)_2O/THF, 6 \text{ hr., reflux}$	52
C_4	$(C_2H_5)_2P-CHCH_2CH_2CH-PC_2H_5$		$C_2H_5OCH=CH(CH_2)_2CH=CHOC_2H_5$	$(C_2H_5)_2O, 10 \text{ hr., 65}$ $THF, 2 \text{ days, 20}$	52 113
18			$(C_2H_5)_2O/THF, 20 \text{ hr., 70}$		52
75			$C_2H_5OH, 8 \text{ days, 20}$		74
6			$(C_2H_5)_2O, 2 \text{ hr., 20; 3 hr., 60}$		74
13			$THF, 1 \text{ hr., reflux}$		300, 301
35			THF		299
26			$C_2H_5OH, 5 \text{ days, 20}$		74
50			$4-C_2H_5OH, 5 \text{ hr., 25}$		302
17			$(C_2H_5)_2O, 26 \text{ hr., 20, 3 hr., 60}$		74
93			$(C_2H_5)_2O, 14 \text{ hr., 65}$		185
15			$(C_2H_5)_2O/THF, 1 \text{ hr., reflux}$		52
			C_2H_5OH		212
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			$THF, 4 \text{ hr., reflux}$		209
			C_2H_5OH		212
			C_2H_5OH		212

TABLE VI—Continued
OLEFINS PREPARED BY THE WITTIG REACTION
B. *Bis-ylides as Starting Materials—Continued*

Ylide	Product	Yield, %	Solvent, Time, Temperature, °C.	References
$C_6(C_2H_5)_2P \cdot CH(CH_2)_2CH=PC_6H_5$	$CH_3-CH(CH_2)_2CH=CH_2$	45	$(C_2H_5)_2O$	189, 188
$C_6(C_2H_5)_2P \cdot CH(CH_2)_2CH=CH-C_6H_5$	$o-C_6H_4(CH=CHC_6H_5)_2$	84	C_2H_5OH , 30 min., 20; 2 hr., reflux	201a
$C_6(C_2H_5)_2P \cdot CH(CH_2)_2CH=CH-C_6H_5$	$o-C_6H_4(CH=CHC_6H_5)_2$	53	C_2H_5OH , 30 min., 20; 4 hr., reflux	201a
$C_6(C_2H_5)_2P \cdot CH(CH_2)_2CH=CH-C_6H_5$	$p-C_6H_4(CH=CH_2)_2$	42	$(C_2H_5)_2O$	188, 189
$C_6(C_2H_5)_2P \cdot CH(CH_2)_2CH=CH-C_6H_5$	$p-C_6H_4(CH=CH_2)_2$	56	C_2H_5OH , 2 hr., 20	108
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	32	C_2H_5OH , 1 hr., 80	66
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	86	C_2H_5OH , 2 hr., 20	193
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	13	C_2H_5OH , 1 day, 20	103
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	83	C_2H_5OH , 1 day, 20	103
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	60	C_2H_5OH , 1 day, 20	103
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	81	C_2H_5OH , 12 hr., 20	193
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	61	C_2H_5OH , 12 hr., 20	193
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	88	C_2H_5OH , 12 hr., 20	210
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	70	C_2H_5OH , 12 hr., 80	66
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	65	C_2H_5OH , 12 hr., 20	210
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	72	C_2H_5OH , 12 hr., 20	193
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	83	C_2H_5OH , 12 hr., 20	210
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	Quant.	C_2H_5OH , 12 hr., 20	210
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	13	C_2H_5OH , 12 hr., 20	210
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	Quant.	C_2H_5OH , 12 hr., 20	210
$p-C_6H_4(CH=CH-C_6H_5)_2$	$p-C_6H_4(CH=CH-C_6H_5)_2$	35	C_2H_5OH , 2 hr., 20	198

	$C_2H_5OH, 2 \text{ hr., } 20$	199
	$C_2H_5OH, 2 \text{ hr., } 20$	199
	46-48 C_2H_5OH	190
	24 $C_2H_5OH, 14 \text{ hr., reflux}$	201a

Note: References 371 to 404 are on p. 490.

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